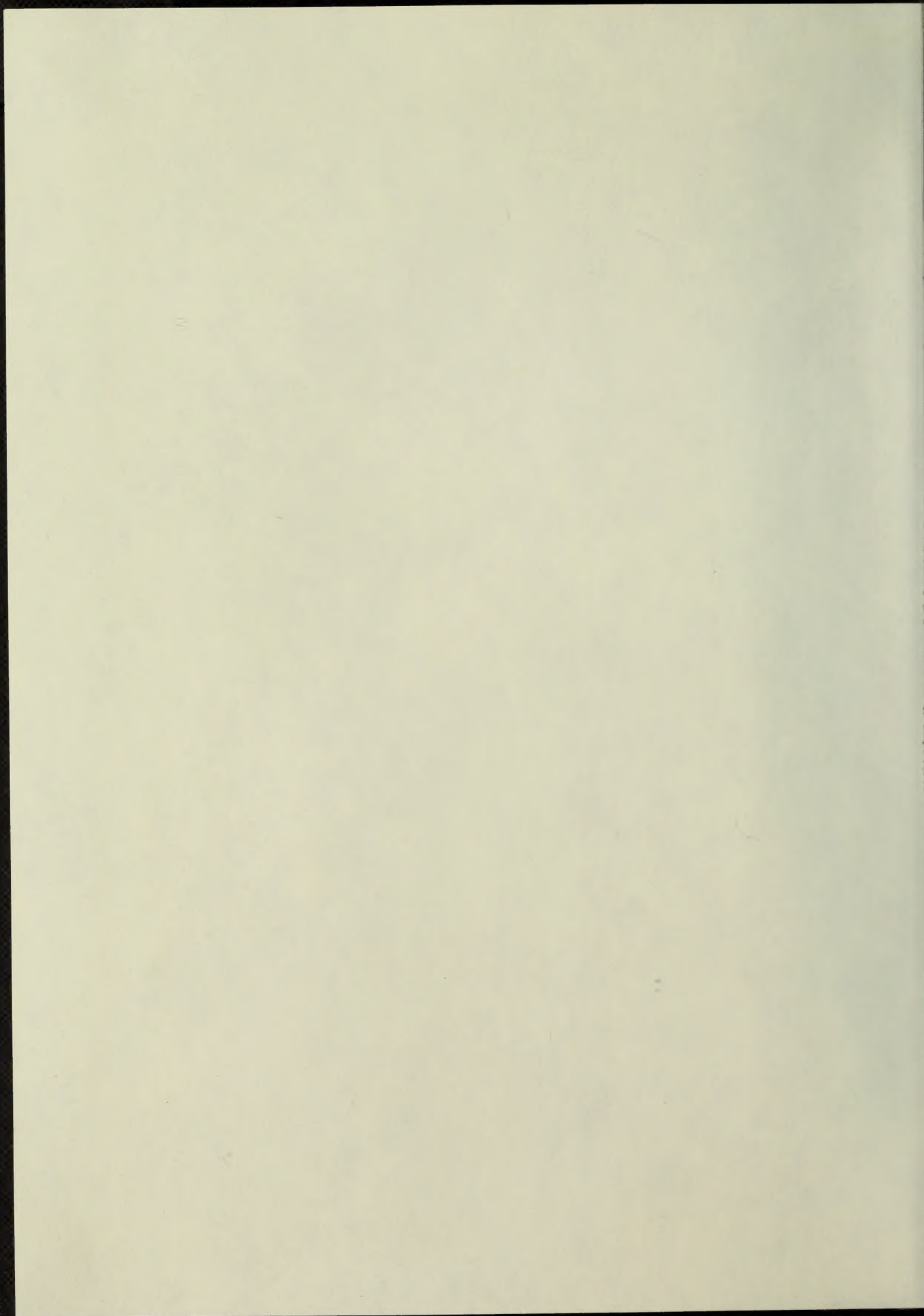
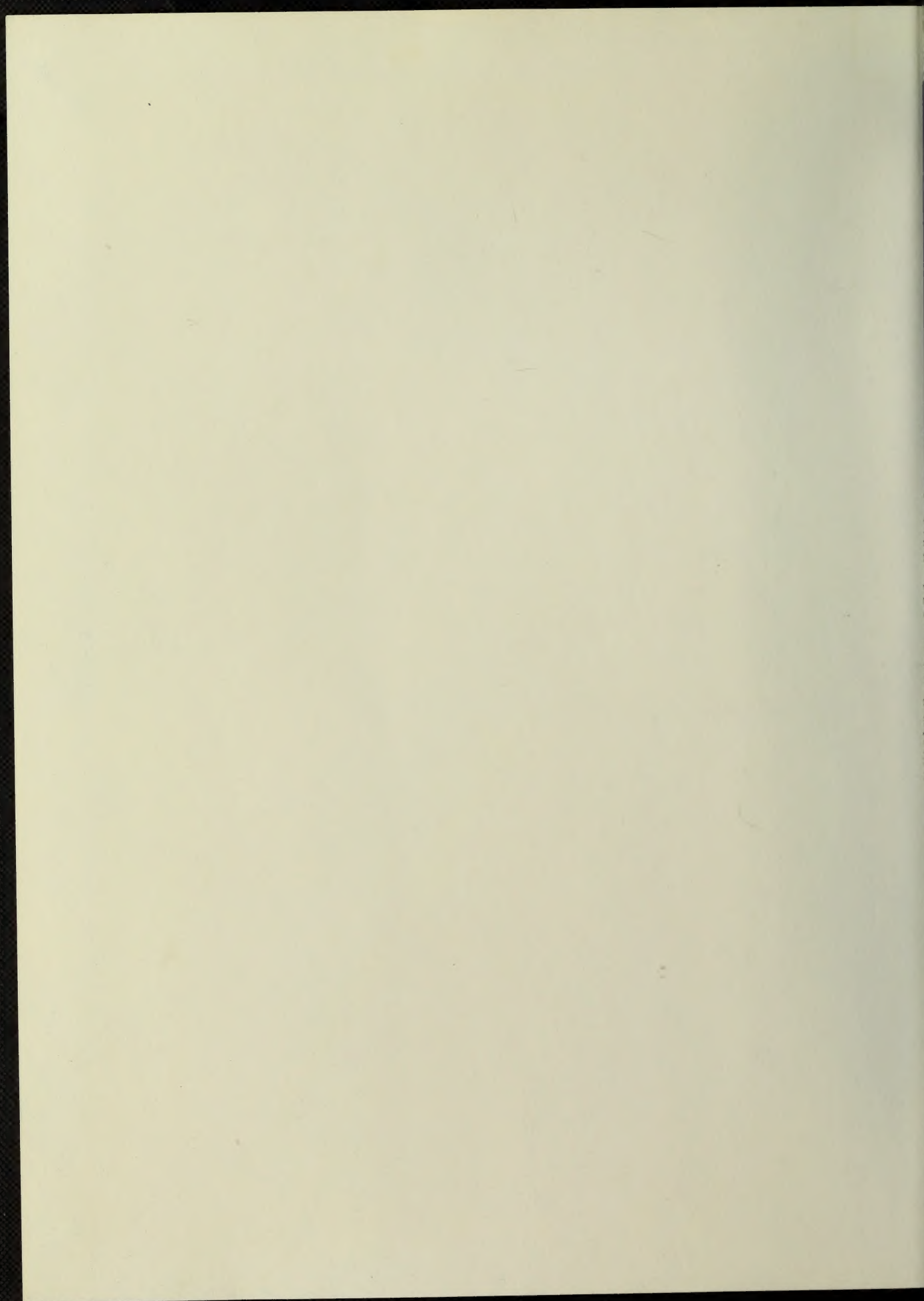


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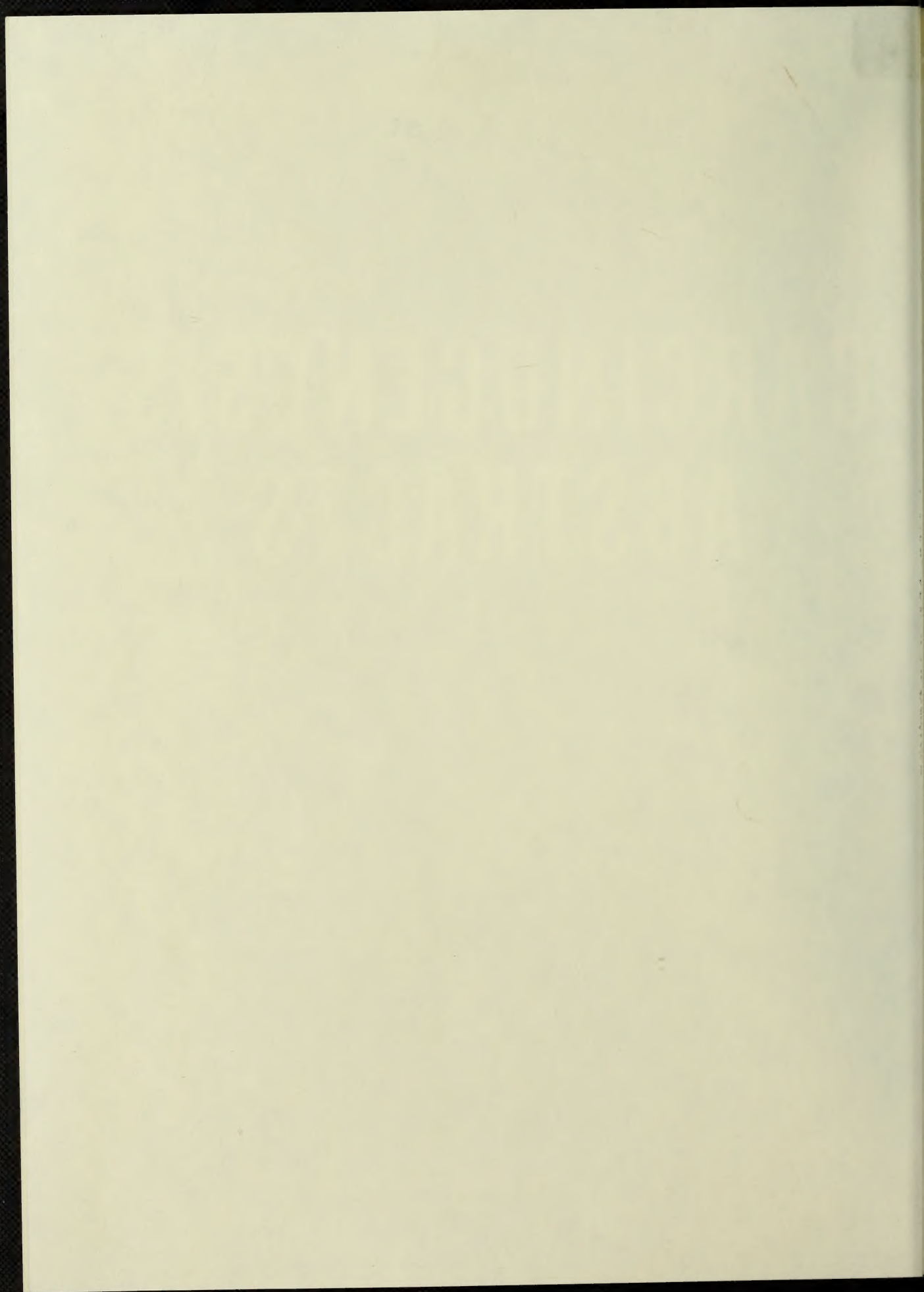
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Abstracts of papers presented at the
National Cancer Institute

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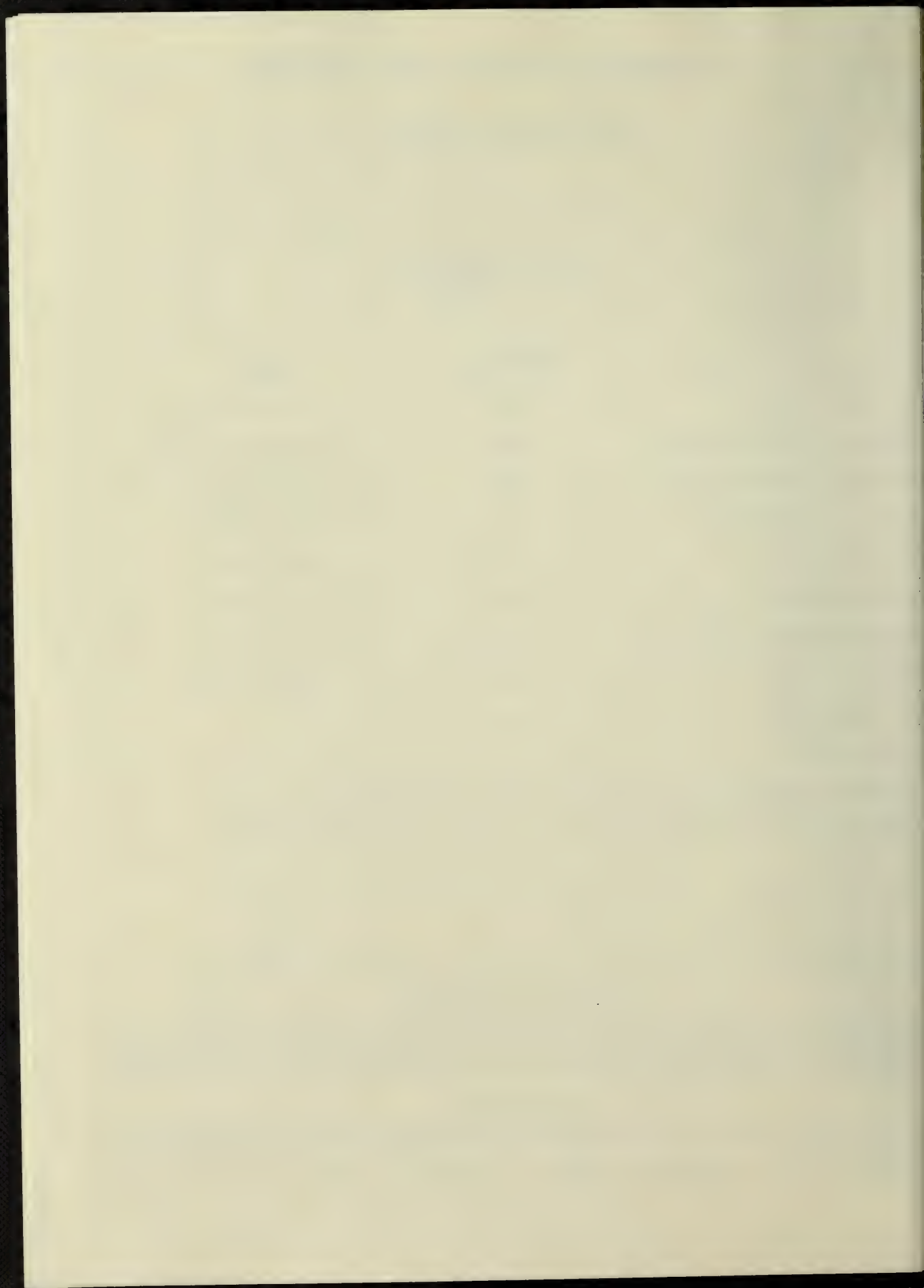
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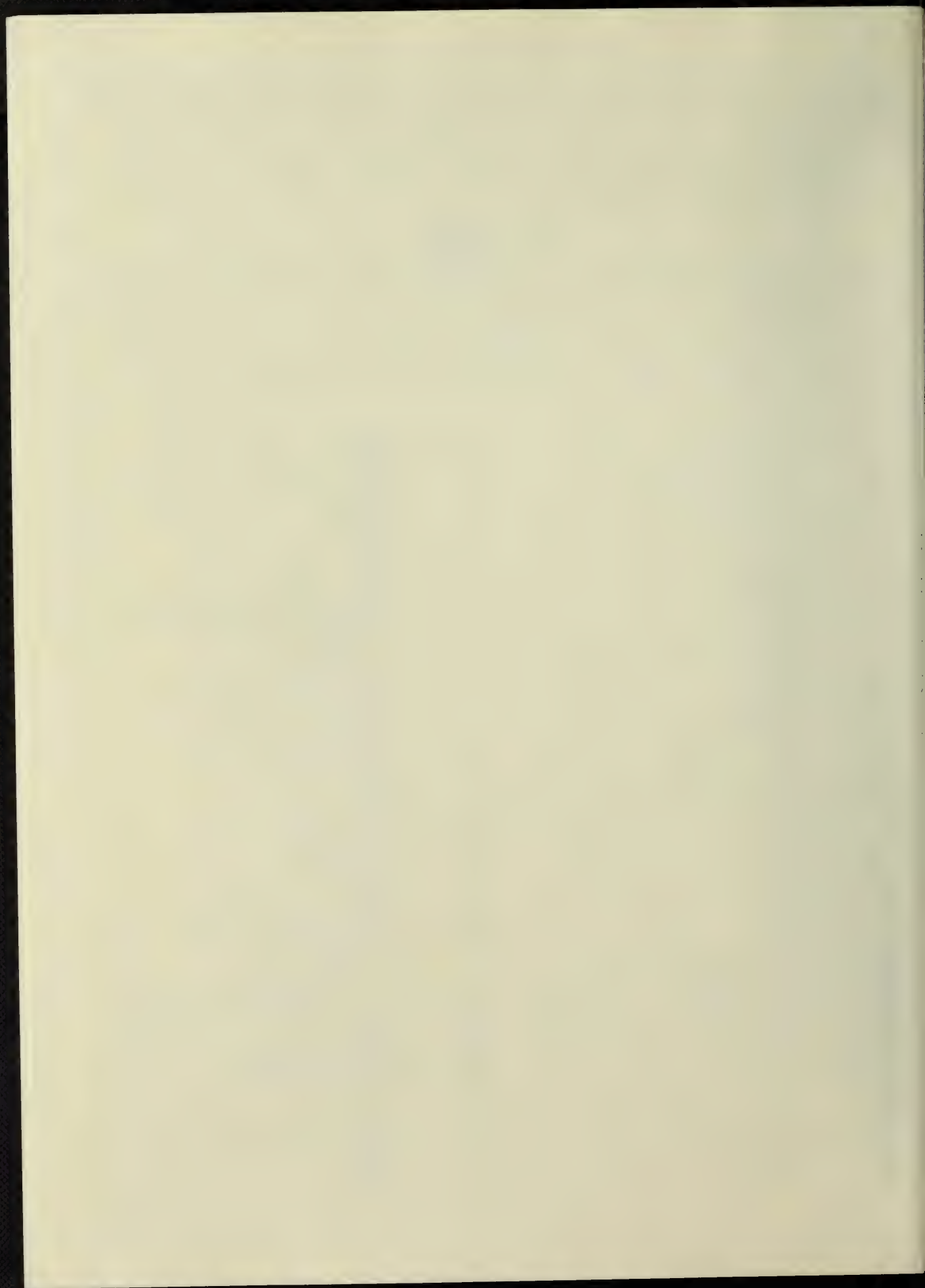
ABBREVIATIONS

JOURNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

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ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		



REVIEW

- 77-0001 Therapy-linked Leukaemia.** (Eng.) Anonymous (No affiliation given) *Lancet* 1(8010): 519-520; 1977.

The possible association of development of acute leukemia in patients treated with cytotoxic drugs for other neoplasms (myeloma, chronic lymphatic leukemia, Hodgkin's disease) is discussed. Acute myeloblastic leukemia (AML) has been reported after chemotherapy for cancer of the breast, lung and ovary, and after immunosuppressant therapy for nonneoplastic diseases. Monitoring of bone-marrow function might be a useful early warning of developing leukemia. Probably antimetabolic instead of alkylating agents should be used when there is a choice. (26 refs.)

- 77-0002 Inhibition of Chemical Carcinogenesis by Antioxidants and Some Additional Compounds.** (Eng.) Wattenberg, L. W. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975.* The Princess Takamatsu Cancer Research Fund. (Tokyo, Japan): pp. 153-166; 1976.

A variety of inhibitors of chemical carcinogens, particularly antioxidants, are described. Compounds that inhibit skin tumor formation in mice include hydrolyzing halogens, compounds that are metabolized to mercapturates, the anhydrides of α , β -unsaturated dicarboxylic acids, and several low molecular weight aromatic hydrocarbons. Of the antioxidants, most work has been done with the phenolic antioxidants, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT). In studies in which BHA or BHT were added to the diet, along with benzo(a)pyrene (BP), it was found that a concentration of 5 mg/g diet of either antioxidant inhibited the carcinogenic effect of BP (1 mg/g diet) on the forestomach of the mouse. Another antioxidant capable of inhibiting polycyclic hydrocarbon-induced carcinogenesis of the forestomach is 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline, which is an additive in commercial animal diets. Disulfiram, dimethyldithiocarbamate, and cysteamine have been shown to be inhibitors of mammary tumor formation resulting from administration of dimethylbenz(a)anthracene (DMBA). Two naturally occurring sulfur-containing antioxidants, benzyl thiocyanate and benzyl isothiocyanate, were able to inhibit mammary tumor formation in female Sprague-Dawley rats when administered in the diet for 1 wk or when given by oral intubation 4 hr prior to administration of a carcinogenic dose of DMBA. Sodium selenide was able to suppress or inhibit the development of epidermal neoplasia. It is not known whether any of the inhibitors exert an effect on human exposure to carcinogens, but BHA and BHT, which are widely used as food additives, might have such an effect. (36 refs.)

- 77-0003 The Metabolism of Chemical Carcinogens to Reactive Electrophiles and Their Possible Mechanisms of Action in Carcinogenesis.** (Eng.) Miller, E. C.; Miller, J. A. In: *Chemical Carcinogens. American Chemical Society Monograph 173.* Searle, C. E., ed. (Washington, D.C.: American Chemical Society): pp. 737-762; 1976.

Current data and concepts on the active forms of chemical carcinogens and their reactions with cellular constituents in the induction of neoplasia are reviewed. N-Hydroxy metabolites have been strongly implicated as proximate carcinogenic derivatives of aromatic amines and amides. In a variety of studies, N-hydroxy metabolites generally proved more carcinogenic than the parent compounds. The sulfuric acid ester of N-hydroxy-2-fluorenylacetamide is a major ultimate carcinogenic metabolite in the rat liver, but other ultimate electrophilic derivatives are also probably involved in the carcinogenicity of this compound. The mutagenicity of the nitroso compounds related to a number of carcinogenic aromatic amines and amides, especially 2-nitrosofluorene, suggests the possible importance of these compounds in carcinogenesis. In the case of polycyclic aromatic hydrocarbons, present data indicate that the precursors of DNA-bound hydrocarbon products formed in vivo are epoxides of dihydrodiols and not K-region epoxides, as had been previously thought. The ultimate carcinogenic metabolites of safrole (4-allyl-2-methylenedioxybenzene) include 1'-hydroxysafrole, 1'-oxosafrole, and the 2', 3'-epoxides of safrole, 1'-hydroxysafrole, and 1'-oxosafrole. The major metabolic precursor of the DNA- and RNA-bound derivatives in the livers of rodents administered aflatoxin B₁ is its 2,3-oxide, which appears to be very labile and, thus, could not be isolated after presumed synthesis by chemical or enzymatic procedures. Both genetic and epigenetic mechanisms of chemical carcinogenesis must be considered, and each may be predominant in specific cases. (211 refs.)

- 77-0004 Molecular and Cellular Mechanisms in Nervous System-Specific Carcinogenesis by N-Ethyl-N-nitrosourea.** (Eng.) Rajewsky, M. F. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975.* Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 313-334; 1976.

The molecular and cellular mechanisms involved in nervous system (NS) carcinogenesis by N-ethyl-N-nitrosourea (ENU) are reviewed. Following a single dose (25 or 75 mg/kg ip) of ENU to BDIX rats during the perinatal age, which is characterized by highly proliferative matrices in the brain, a high incidence of neuroectodermal neoplasms occurred in the central and peripheral NS. The tissue-specific car-

cinogenicity of ENU seems to depend on the proliferative and/or differentiative state of the cells at the time of exposure. Studies of the elimination of ethylated purine bases from the DNA of high-risk (perinatal brain) and low-risk (liver and adult brain) rat tissues indicated that the selective persistence of O⁶-ethylguanine could increase the probability of malignant transformation and explain the NS specificity of ENU. Further studies using dimethylnitrosamine (DMN) have shown that the enzyme system responsible for the elimination of O⁶-alkylguanine from DNA either has a limited capacity or is inhibited by high doses of alkylating carcinogen. Single cell suspensions of fetal BDIX rat brain cells (FBC), transferred to culture 20-90 hr after a transplacental pulse of 75 µg/g of ENU on the 18th day of gestation, became tumorigenic after about 200 days. The characteristic sequence of phenotypic alterations in the cultured FBC before cell proliferation is described. The possibility of using this "in vitro-in vivo" system to clarify events occurring between primary carcinogen-cell interaction and the onset of clonal tumor growth and to characterize the type and differentiated state of FBC demonstrating neoplastic transformation is summarized. (78 refs.)

- 77-0005 Replication and Repair of DNA in Liver of Rats Treated with Dimethylnitrosamine and with Methyl Methanesulphonate.** (Eng.) Craddock, V. M. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, R. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 293-311; 1976.

Treatment of rats with dimethylnitrosamine (DMN) at varying intervals after partial hepatectomy provides a system for studying how DMN induces cancer. Both DMN and nitrosomethylurea (NMU) induced the highest incidence of tumors when given 24 hr after the operation, the time of maximum DNA synthesis; however, methyl methanesulfonate (MMS), which damages DNA in a similar way, did not induce liver tumors. Therefore, not only are DNA damage and cell replication necessary for the initiation of cancer, but the genetic damage must be of a certain type. The difference between regenerating and intact adult liver, in which cancer is not usually induced after a single administration of DMN, seems due to the fact that in regenerating liver the damaged DNA is stimulated to replicate. Although the extent of replication was reduced by DMN, DNA synthesis continued at a higher rate than that of normal intact liver and occurred at a time when alkylation damage was present. Differences in response to DMN and MMS are possible due to differences in the type of damage, rate of repair, and/or enzyme induction. In the case of MMS, damage to DNA does not include formation of the mispairing base, O⁶-methylguanine. To distinguish between de novo and repair-type replication, a new technique was used to study DNA replication in the intact animal. This method is based on the fact that nuclei enlarge during replication due to an influx of acidic proteins from the cytoplasm (S-phase), and, therefore, they can be separated

from nonreplicating nuclei by rate zonal centrifugation. When animals were injected with ³H-thymidine (TdR) after carcinogen treatment, S-phase nuclei showed ³H incorporation, representing de novo synthesis. In contrast, ³H incorporation into noncycling nuclei following treatment with ³H-TdR and hydroxyurea (HU) represented excision repair. Repair replication was induced by DMN treatment in intact animals. In partially hepatectomized animals treated with DMN, de novo replication occurred. Thus, replication before excision repair could be responsible for carcinogenesis. (33 refs.)

- 77-0006 N-Nitroso Compounds. Analysis and Possible Carcinogenicity in Man.** (Fre.) Gričute, L. (Service des Cancérogènes de l'Environnement, Centre International de Recherche sur le Cancer, 150, cours A. Thomas, 69008 Lyon, France) *INSERM Symposia Series* 52(13): 375-385; 1976.

The role of N-nitroso compounds in human pathology has still to be elucidated. Although experimental data cannot be extrapolated to the human situation, there is indirect evidence that nitroso compounds can be carcinogens in man. Although some nitrosamines are organ-specific, the nitroso group induces the development of many different types of cancer in animals. It is probable that the same phenomenon occurs in human pathology. A possible approach to the study of the role of nitrosamines in human pathology would be to establish a correlation between cancer morbidity in some regions and amounts of N-nitroso compounds in the environment. In view of the complexity of the problem of in vivo nitrosamine formation, it is more realistic to measure exogenous nitrosamines. Many laboratories are currently engaged on studies of N-nitroso compounds, although systematic information on their presence in the environment is scant. The data acquired by different laboratories has been obtained using a variety of methods for sampling, storage, clean-up and identification and estimation, with the result that it is not known to what extent these results are comparable. Therefore, the standardization and determination of comparability of methods for the identification of N-nitroso compounds is the first step towards their quantitation in the environment. Adequate methods are now available for the determination of volatile nitrosamines, down to the µg/kg level, but methods for non-volatile nitrosamines are still in the development stages. In order to avail all interested laboratories of information on analytical methods for volatile nitrosamines, IARC's analytical chemistry laboratory has organized a three part collaborative study using samples of canned luncheon meat. The European Sub-Committee for the Guidance of Collaborative Studies, at its last meeting, recommended that such studies be continued and extended to include non-volatile nitrosamines. In parallel with the perfection of analytical techniques, IARC has initiated studies on the measurement of volatile nitrosamines in the environment in conjunction with the epidemiological studies on esophageal cancer presently being performed. The data collected up to now is far from complete but it does represent the first step towards the

evaluation of the risk to health of N-nitroso compounds. (27 refs.)

77-0007 Carcinogenic and Mutagenic N-Nitroso Compounds. (Eng.) Lijinsky, W. In: *Chemical Mutagens. Principles and Methods for Their Detection*. Hollaender, A., ed. (New York: Plenum Press): Vol 4, pp. 193-217; 1976.

Carcinogenic and mutagenic compounds are discussed, including the significance of the formation of N-nitroso compounds in the environment. The carcinogenicity of N-nitroso compounds is discussed in terms of experiments in rodents and other species, the organ-specific effects, and the relation of chemical structure to carcinogenic activity. A discussion on the mutagenesis by N-nitroso compounds covers direct action in microorganisms, the metabolic conversion of nitrosamines into mutagens, and mutagenesis of multicellular organisms. Topics of the metabolic conversion of nitrosamines include the host-mediated assay, in vitro studies with microorganisms, and in vitro studies with cultured mammalian cells. The importance of nitroso compounds as biologically active agents is discussed in terms of nitroso compounds as a model for studies of carcinogenesis, the comparative metabolism of nitroso compounds, the mechanism of action of N-nitroso compounds, mutagenesis as a model for carcinogenesis, and additive and inhibitor biological effects of nitroso compounds. The human exposure to nitrites and nitrosamines should be reduced. High levels of residual nitrite should not be allowed in foods in which no botulism hazard exists; the use of the minimum amount of nitrite needed for flavor and, to a lesser extent, for color should be allowed. (102 refs.)

77-0008 Carcinogenic Risk from Nitrite, Nitrate and N-Nitrosamines in Food. (Eng.) Swann, P. F. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., Mortimer St., London W1P 7PN, England) *Proc R Soc Med* 70(2): 113-115; 1977.

The carcinogenic risk from N-nitrosamines, nitrates, and nitrites in food was evaluated. Nitrites can react readily with amines and amides to form N-nitroso compounds, most of which are highly carcinogenic. Nitrates do not react in this way, but they can be reduced to nitrites, commonly by bacteria. This occurs during bacterial spoilage of nitrate-containing food and, also, in the mouths of adults and the upper gastrointestinal tract of infants. Nitrosamines have been found in human food, and the nitrosation reaction, which proceeds rapidly in weak acid, can also occur when dietary amines and nitrite are mixed in the stomach. There is now evidence that the nitroso compounds owe their carcinogenicity to their ability to be converted in vivo into alkylating agents that react with cellular components. Studies of the alkylation of cellular components have recently become focused on the alkylation of the O⁶-position of guanine in

DNA. If it is finally proved that this reaction is responsible for the carcinogenicity of these compounds, it will provide a conceptual basis for an understanding of the cumulation of carcinogenic doses and the cooperation between carcinogens. (21 refs.)

77-0009 Nitrates and Gastric Carcinoma. (Ger.) Thaler, H. (4. Medizinische Abteilung, Wilhelminenspital, Montleartstr. 37, A-1171 Vienna, Austria) *Dtsch Med Wochenschr* 101(47): 1740-1742; 1976.

General discussions are presented on the increased incidence of gastric cancer in Japan and Chile and the possible hazards of long-term isosorbide dinitrate treatment of patients with coronary insufficiency. In Japan, the high gastric cancer incidence is due to the regular consumption of vegetables with a high nitrite and nitrate content and of fish, which is a source of secondary amines. Nitrites and secondary and tertiary amines react in the stomach to form carcinogenic nitrosamines. In Chile, the high incidence of gastric cancer is due to the intense use of nitrate fertilizers, which are reduced to nitrites by microorganisms. The nitrites are taken up from the drinking water and plants. Nitrosamines are synthesized from these nitrites and amines in the stomach. The long-term use of isosorbide dinitrate does not appear to increase cancer risk, because achlorhydria would be required for reduction of the nitrate to nitrite in the gastric juice, but the synthesis of nitrosamines from these nitrites would require normal gastric juice. Consequently, nitrate reduction and nitrosamine synthesis in the gastric juice mutually preclude each other. (8 refs.)

77-0010 Possibilities for Prevention of Large Bowel Cancer. (Eng.) Williams, R. E.; Hill, M. J.; Drasar, B. S. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Princess Takamatsu Symposium. (Tokyo): pp. 143-151; 1976.

Statistical studies are cited that attribute a high incidence of large bowel cancer to a high dietary consumption of meats and fats, which affect the substrates available to the gut bacteria and the bacterial species present. The major factor in the etiology of this disease might be the production of a carcinogen or cocarcinogen from bile acids by the gut microflora (Clostridia, Bacteroides). *Clostridium paraputrificans*, *C. tertium* and *C. indolis* produce a partially desaturated acid steroid by dehydrogenation of bile steroids. Preventive measures proposed were: reduction of steroids reaching the gut; reduction of bacterial action on the steroids; and protection of the colon mucosa. A study was proposed to ascertain if high levels of acid steroids, or large numbers of Clostridia containing dehydrogenating enzymes in the feces of healthy individuals might be used as a screening method to detect the development of large bowel cancer. (19 refs.)

- 77-0011 Relation of the Characteristics of Liver Cells During Culture, Differentiation, and Carcinogenesis.** (Eng.) Ichihara, A. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 317-327; 1976.

The expression of isoenzymes of branched-chain amino acid transferase in normal rat liver and in Morris hepatomas is discussed. Isoenzyme I was present in fetal, normal adult, and regenerating liver; fast- and slow-growing hepatoma; and heart, kidney, spleen, muscle, and testis. Isoenzyme II was found only in normal or regenerating liver and slow-growing hepatomas. Enzyme III was expressed in the hepatomas and also brain, placenta, and ovary. Benign liver adenomas induced in rats fed 3'-methyl-4-dimethylaminoazobenzene for 2-4 mo had the isoenzyme pattern of normal liver, but the hepatomas induced after 5 mo of feeding expressed enzymes I and III. Studies of cultured hepatocytes demonstrated that loss of chromosome number, neoplastic transformation, and enzyme III were closely correlated. Immature hepatocytes could be propagated and transformed in vitro more easily than could mature cells. The possible origin of liver cells that can be induced to proliferate in culture is discussed. (80 refs.)

- 77-0012 Nutrition and Cancer.** (Ger.) van der Linde, F. (Zürcher Krebsregister, Nelkenstr. 15, CH-8006 Zurich, Switzerland) *Zentralbl Bakteriologie [Orig B]* 163(1/4): 128-152; 1976.

The problem of a relationship between nutrition and cancer has to be approached from two different points of view: direct effect of carcinogens present in foods or in food additives (direct carcinogenesis) and in vivo synthesis of carcinogens caused by changes in metabolism due to altered dietary habits (indirect carcinogenesis). The effects of nutritional deficiency and nutritional excess must be distinguished for the second mechanism. In man, possible relationships between nutrition and cancer are postulated mainly for tumors of the gastrointestinal tract and for hormone-dependent cancers. Epidemiological evidence points to the major importance of indirect carcinogenesis caused by specific nutritional deficiencies and excesses. As experimental studies in man are difficult to perform, most hypotheses are based on statistical associations; caution is required in drawing inferences on causal relationships. Cancers of the upper and lower gastrointestinal tract epidemiologically behave in a different way, the former showing a marked decrease in most western countries, the latter a slight increase. The etiology of cancers of the esophagus and stomach has yet to be determined. Migrant studies show a major effect of environmental rather than genetic factors. Substantial differences in dietary habits between countries with high and low incidence of stomach cancer point to the importance of nutrition as an etiological factor; no specific dietary components have been identified so far. Recent hypotheses suggest that dietary factors may relate to cancer of the colon by their effect on bile production and on the bacterial makeup of feces, which in turn might be transforming bile

acids into active carcinogens. There is, however, disagreement about the specific dietary component responsible for this model of carcinogenesis. Lower consumption of dietary fiber may result in retarded bowel function and additional time for bacterial proliferation and degradation by bacteria of bile acids. It is also hypothesized that increased bile acid and neutral sterol excretion and microbial modification of these compounds with the high content of animal fat in the western diet may cause this bowel cancer. With hormone-dependent cancers, a correlation has been shown between body wt and height and breast cancer as well as between obesity and cancer of the endometrium. Some dietary aspect may cause a hormone metabolism change responsible for increased cancer risk. (126 refs.)

- 77-0013 Nutritional Modulation of Carcinogenesis.** (Eng.) Newberne, P. M.; Rogers, A. E. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Research Fund, Tokyo, 1975*. The Princess Takamatsu Cancer Research Fund. (Tokyo, Japan): pp. 15-40; 1976.

Nutrients that appear to modulate susceptibility to cancer are discussed. In New York City, patients with esophageal cancer tend to be heavy smokers with high alcoholic consumption and decreased consumption of milk, eggs, and green leafy vegetables. Dietary factors are associated with esophageal cancer in each of the areas of high incidence. Gastric cancer exhibits a high incidence in Japan, Chile, Columbia, Austria, Iceland, and Finland and a low incidence in the United States and Canada. Several dietary factors have been implicated, but studies of the food habits in gastric cancer patients have shown few significant differences in the intake of specific nutrients when compared with control groups. The incidence of colon cancer is associated with a western style diet and a higher standard of living. Hepatocarcinoma is associated with cirrhosis resulting from complex interactions of diet, toxins, and possibly viral liver disease. Increased unsaturated lipid in the diet of experimental animals results in an increased incidence of liver tumors. Induction of liver tumors is enhanced if the diet is both high in fat and deficient in the lipotropes choline, methionine, and folic acid. Breast cancer incidence is correlated with socioeconomic status and therefore with overnourishment. The incidence of breast cancer is low in developing societies and in Japanese women but increases in these population groups when they migrate to the United States. Nutrition offers an acceptable and direct means to attack the cancer problem in human populations. (83 refs.)

- 77-0014 Factors Modifying Carcinogenesis.** (Eng.) Newberne, P. M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 7-12; 1976.

Dietary factors modifying carcinogenesis are reviewed. Talc, asbestos, and high consumption of raw vegetables have been

associated with the high incidence of gastric cancer in Japan. Diets high in protein and/or fat and low in fiber are consumed by populations having a high incidence of colon cancer. A diet high in fat and marginal in lipotropes increased colon carcinoma from dimethylhydrazine in rats. Primary liver cancer is a major problem in some populations of Africa, south China, Hawaii and Thailand. Among the Bantu, the age specific incidence is 500-fold that in the United States. In rats, a high fat diet deficient in choline and methionine enhances chemical carcinogenesis in the liver. (29 refs.)

- 77-0015 Problems of Establishing the Toxicological Risks Represented by Foreign Substances in Food.** (Ger.) Henschler, D. (Institut für Pharmakologie und Toxikologie, Universität Würzburg, Versbacher Landstr. 9, D-8700 Würzburg, W. Germany) *Zentralbl Bakteriol [Orig B]* 163(1/4): 118-127; 1976.

The toxicological examination of foreign substances found in foods runs into a series of general and toxicological difficulties in addition to food-specific problems. The determination of limit doses or concentrations that cause just detectable or no noxious effects presents a rather general problem. Efforts are being made to derive tolerance values for the concentration in the individual foodstuff and for the av max uptake during a unit of time from these "effect thresholds." Dose/effect relationships, which are relatively easy to ascertain for acutely toxic effects, are difficult to determine accurately for the chronic action of very small doses of additives. The initial section of the dose/effect curves manifests a very flat course; the real start of the effect can only be formulated in terms of probability even when supported by large numbers of animal experiments. Differences in the type and intensity of additive-produced effects from species to species make it difficult to draw a clear line between what is injurious to human health and what is not. In the case of carcinogenic, mutagenic and teratogenic effects, which cannot be evaluated as the usual toxic effects on account of a long induction time and substance or individual specific sensitivity of phase, special criteria must be used. The question as to whether ineffective or innocuous limit doses can be indicated or not still needs clarification. Special problems arise in the case of small concentrations of food additives because no experience has been gained on toxic effects on humans. Food additives are ingested in such small quantities that neither acute poisoning ensues nor do interrelationships become apparent from epidemiological examinations. The effects on test animals and man are not readily comparable because the small rodents differ in their digestive mechanisms from man. The administration of the substances in the drinking water or the standard diet can hardly be compared with their somewhat discontinuous uptake in certain foodstuffs by humans. In addition, intermediate metabolism of the small rodents differs from that of humans. Attempts are made to eliminate these difficulties when establishing tolerance values by introducing a so-called "safety margin." These are not completely successful. The essential tasks incumbent upon science are as precise a quantification of the risks as possible with research concentrating

on the recognition of the real dangers. This objective is better accomplished by the mechanistically oriented research into the effects of the various additives rather than by compliance with rigid test regulations. (4 refs.)

- 77-0016 Atmospheric Mutagens.** (Eng.) Fishbein, L. In: *Chemical Mutagens. Principles and Methods for Their Detection*. Hollaender, A., ed. (New York: Plenum Press): Vol. 4, pp. 219-319; 1976.

The source and effect of atmospheric mutagens on man are discussed. Various pollutants are the products of man's own waste: sulfur oxides, nitrogen oxides, polynuclear aromatic hydrocarbons, peroxyacyl nitrates and miscellaneous oxygenated derivatives. Many of these compounds, such as benzo[a]pyrene and dibenzanthracene, are mutagenic. Drastic disturbances in respiratory function have been attributed to ozone, and a variety of studies have indicated that it is a general mutagenic agent. Various halogenated hydrocarbons with mutagenic properties have now been located throughout the world. These hydrocarbons include fluorocarbons, vinyl chloride, trichloroethylene, tetrachloroethylene, carbon tetrachloride, miscellaneous halogenated hydrocarbons, and bromoalkanes. Fluorine, another mutagen that is worldwide in distribution, is prevalent in urban settings. Studies have shown the mutagenic potential of sodium fluoride in a variety of female mammalian germ cells. Other mutagenic compounds that are discussed are pesticides and related compounds (DDT and its metabolites, dichlorvos, formaldehyde and ethylene oxide) and polychlorinated biphenyls and aerosols (lead, mercury). Information is sparse or lacking on many of these mutagens and on aspects of their transport, residence times, and stability. The fate and mutagenic hazard to man of many of these compounds, particularly halogenated hydrocarbons, is speculative. (606 refs.)

- 77-0017 Water Pollution and Cancer Risk.** (Fre.) Aubert, J. (Groupe de Recherches INSERM U.40 de Biologie et d'Océanographie Médicale, CERBOM, Parc de la Côte, 1, avenue Jean Lorrain, 06300 Nice, France) *INSERM Symposia Series* 52: 95-103; 1976.

Carcinogenic chemicals likely to occur as pollutants of fresh water or seawater are reviewed. The carcinogens may exist naturally in the water supply, as is the case with arsenic in the province of Cordoba, Argentina, or they may be industrial or agricultural contaminants. Nitrosamines, for example, are derived from pesticide residues of nitrates and nitrites, and the presence of phytoplankton or aquatic plants in the water favors their synthesis. High levels of aromatic hydrocarbons are detectable in the water of areas with high atmospheric pollution, and some of these compounds are readily concentrated by marine organisms, such as clams. The polychlorobiphenyls (PCB), which have been recently proved carcinogenic in laboratory animals, have been detected in the water of the North Atlantic Ocean, and they can also be concentrated by aquatic organisms. PCB's enter into the

composition of plastics, paints, varnishes, adhesives, and many other industrial products. The precise evaluation of the potential health hazards of carcinogenic water pollutants remains undetermined. (19 refs.)

77-0018 Environmental Risks Related to Cancer. (Eng.)

Peacock, P. B. In: *Cancer: The Behavioral Dimensions*. Cullen, J. W.; Fox, B. H.; Isom, R. N., eds. (New York: Raven Press): pp. 85-92; 1976.

Environmental risks related to the incidence of cancer are discussed. Cigarette smokers are at a greatly increased risk of lung cancer as compared with nonsmokers. Lung cancer also shows an urban excess, particularly among men; however, this has not been definitely correlated with air pollution. Asbestos is highly carcinogenic for lung cancer. Compared with the risk of cigarette smoking, the effects of occupational exposures and air pollution are small. In experimental animals, an increased uptake of fat increases the yield of breast cancer; animals on a high fat diet are also more likely to get breast cancer when exposed to chemical carcinogens. There is a strong correlation between high fat diets and increased breast cancer in women. There is a similar correlation between cancer of the colon and fat intake; cancer of the kidney and possibly of the prostate may follow such a pattern. There is probably more than one carcinogenic pathway when dealing with cancer of the colon and fat. It has not yet been proved whether there is a correlation between a lack of dietary fiber and large bowel cancer. Cholestyramine, used to reduce serum cholesterol levels by increasing the fecal loss of bile acids, may increase the incidence of colon cancer. Consumption of large amounts of salty foods and small amounts of milk may be associated with carcinoma of the stomach. Aflatoxins from *Aspergillus flavus* are strongly associated with hepatic carcinoma. Nitrosamines in foodstuffs and halogenated hydrocarbons in drinking water may be carcinogenic. Estrogens, rauwolfia, alcohol, and reserpine-containing drugs may also be carcinogenic. Excess exposure to UV causes skin cancer. Psychological factors may also be associated with cancer, for example, persons with cancer of the pancreas show extreme states of depression. Priority attention should be given to modification of life-style habits that can be controlled: tobacco usage, incorrect nutrition, and alcohol usage. (49 refs.)

77-0019 Cancer and the Environment. (Eng.) Epstein, S. S. (Sch. Public Health, Univ. Illinois Medical Center, Chicago, IL) *Bull At Sci* 33(3): 22-30; 1977.

Evidence for environmental causes of cancer is reviewed. The validity of data from animal testing, and the factors preventing effective regulation of carcinogens, are discussed. The constraints on reducing cancer incidence appear to be political and economic. Recommendations are: more vigorous pursuit of regulation of environmental carcinogens; insulation of research on carcinogens from political and economic pressure; analysis of the true cost of dispersion of carcinogens into

the environment; and further research on environmental carcinogens. (22 refs.)

77-0020 The Hazard of Asbestos. (Eng.) Anonymous. (No affiliation given) *Med J Aust* 2(16): 588-590; 1976.

Asbestosis was first considered a dust disease like the other pneumoconioses, and recognition of the carcinogenic nature of asbestos came later. From the many reports associating asbestos exposure with later development of pleural mesothelioma, there seems little doubt that the association is a real one, although it is highly improbable that all cases are asbestos-associated. A significant excess of pleural tumors has been found among naval dockyard workers, who had varying amounts of exposure to asbestos of different types. Concentrations of airborne asbestos in ships being refitted have been demonstrated to be high. The term asbestos includes several minerals of different composition but with similar physical properties: amosite, chrysotile, fibrous anthophyllite, and crocidolite (blue asbestos). Crocidolite is the one most often associated with mesothelioma. Unfortunately, most workers with asbestos have been exposed to more than one type. There is considerable evidence of awareness of the asbestos problem both in the industries involved, as evidenced by the recent formation of the Asbestos Association of Australia, and among Australian health and labor authorities. (13 refs.)

77-0021 Arsenic and Skin Cancer. (Eng.) Sanderson, K. V. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 473-491; 1976.

The carcinogenic effect of arsenic is discussed in relation to skin cancer. Whether arsenic acts as a carcinogen by substituting for phosphorus in the nucleic acid molecules, as an enzyme inhibitor, or in some less direct manner is not certain at present. There is evidence, however, that phytohemagglutinin-stimulated lymphocytes have disturbed nuclear division after brief in vitro exposure to dilutions of arsenic in the culture medium and that higher concentrations cause 80% to 100% of the entire metaphase chromosomes to be pulverized. One theory is that arsenic competitively inhibits the insertion of phosphorus into the nucleotide chain, enzymes containing sulfhydryl groups, and the dark repair mechanism for DNA. In view of some of the reputed therapeutic effects of arsenic, it may act partly as an immunosuppressant. Arsenic cancer takes the form of one or more of the following basic classes of neoplasms: keratosis, Bowen's disease, intraepidermal epithelioma of Jadassohn, and squamous cell and basal cell carcinomas. The distinguishing features of arsenic-induced lesions are their multiplicity and distribution. In contrast to most other skin cancers, arsenic lesions are scattered almost at random. (90 refs.)

- 77-0022 **Tar Keratosis.** (Eng.) Gotz, H. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpfort, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 492-523; 1976.

The relationship between tar keratosis and skin cancer is discussed, with particular reference to an epidemiological analysis of 111 tar workers. Tar skin and tar warts may provide the basis for the development of precanceroses and epitheliomas. The tar products act with varying intensity, sometimes causing atrophy of the epidermis and dermal papillae and sometimes causing proliferation in the form of hyperkeratotic tar warts, papillomas, and fibromas. The development of cancer by way of tar skin or tar warts is probably always due to a combined injury. A common provoking factor in the formation of tar warts on the scrotum is the rubbing of tight trousers over coal particles, which causes tiny scratches to develop. UV light also appears to be significant in the formation of tar skin and keratosis and in the transition of these conditions to carcinoma. Erythema threshold determinations in 111 former tar workers who had not been exposed to the injurious tar for an av of 8.8 yr showed that 82% still demonstrated increased UV sensitivity. Workers who had developed cancer showed a much higher percentage of persistent photosensitization (58%) than those who had not had cancer (33%). The damage to skin that is done by tar and its derivatives is due, in part, to the photosensitizing property of certain chemicals such as anthracene, acridine, methylanthracene, pyrene, fluoranthene, and benzpyrene. Among the 111 tar workers, tar warts appeared on sites exposed to light (the face, dorsum of the hand) in 71% of the cases; the next most frequent site was the scrotum (8%). In addition to irritation, the high lipid content of the scrotal skin, which allows for the penetration of fat-soluble carcinogenic tar noxae, is also responsible for increased tar wart and carcinoma incidence in this area of the body. The length of employment before the appearance of tar warts in the sc tar workers was 15 yr. The av latent period before the development of cancer was 20 yr. Skin cancer was found in 46 workers (41%). Thirty-three carcinomas were seen in 80 subjects between the ages of 50 and 65. Thus, about 75% of all tar cancers developed in the age group most disposed to cancer. (52 refs.)

- 77-0023 **Hormone Dependency of Rat Mammary Tumors.** (Eng.) Heuson, J. C.; Legros, N.; Heuson-Stiennon, J. A.; Leclercq, G.; Pasteels, J. L. In: *Breast Cancer: Trends in Research and Treatment. A Monograph of the European Organization for Research on Treatment of Cancer*. Heuson, J. C.; Matthei, W. H.; Rozenzweig, M., eds. (New York: Raven Press): pp. 81-93; 1976.

Mechanisms underlying the hormone dependency of mammary tumors were investigated. Tumors were induced by either a single gastric instillation or an ip injection of 7,12-dimethylbenz(a)anthracene (DMBA) into 50-day-old female Sprague-Dawley rats. Small doses of estradiol-17 β administered sc to ovariectomized tumor-bearing rats were effective in restoring tumor growth, but large supraphysiological doses

were distinctly inhibitory, possibly because of their interference with the stimulating effect of prolactin. When estradiol-17 β (1 μ g/kg) or progesterone (16 mg/kg) was administered to ovariectomized rats in another experiment, progesterone proved equally effective in restoring tumor growth. Estradiol-stimulated tumors closely resembled those growing in nonovariectomized, untreated rats, whereas progesterone-stimulated tumors had totally different cytological and histological characteristics. To analyze the effect of various hormones on DNA synthesis and histological appearance, organ cultures of DMBA tumors received additions of hormones at the following concentrations: insulin 10 μ g/ml, prolactin (ovine) 5 μ g/ml, progesterone 1 μ g/ml, and estradiol 1 μ g or 1 ng/ml. Insulin considerably enhanced DNA synthesis to a variable extent in most tumors. In the presence of insulin, prolactin and progesterone also were stimulatory. Estradiol in combination with prolactin and in the presence of insulin was inhibitory in 4/10 tumors. The tumors were papillary or cribriform carcinomas, and no histological characteristics could be used to predict hormone responsiveness in vitro. The possible use of this experimental model for screening drugs potentially active in breast cancer treatment is discussed. (32 refs.)

- 77-0024 **Androgenic-Anabolic Steroids and Hepatocellular Carcinoma.** (Eng.) Johnson, F. L. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 95-103; 1976.

In humans, there is an increased incidence of hepatocellular carcinoma (HCC) in men beyond puberty, which suggests the possibility of a relationship between androgens and HCC formation. In rodent strains with a high incidence of spontaneous HCC (C3H and CBA mice), the neoplasm is three to six times more common in males. However, the most significant experimental data come from rodent strains in which a direct effect of hormonal manipulation on HCC development has been shown. How androgenic hormones can give rise to hepatic tumors remains unanswered. The simplest concept is that following androgen-induced injury, compensatory liver cell hypertrophy occurs. If this becomes uncontrolled, a malignant HCC results. However, many factors affect the influence of hormones on the formation of hepatomas. It has been hypothesized that androgens predispose to HCC and estrogens to benign hepatic adenoma, but the situation may be far more interrelated than this. What has been observed may well be a spectrum of basically androgenic-induced liver changes, with a HCC-like lesion on one end of the spectrum, a lesion with an as yet undefined malignant potential, and benign adenoma of the liver at the opposite end. In mice, norethynodrel, norethisterone, and norethisterone plus mestranol increased the occurrence of hepatoma in males. In female mice, norethynodrel produced hepatic cellular swelling with sinusoidal aberrations, but not hepatomas. (40 refs.)

- 77-0025 **Breast Cancer and Thyroid Therapy. Statement by the American Thyroid Association.** (Eng.) Gorman, C. A. (Education Committee, American Thyroid

Assoc., Mayo Clinic, Rochester, MN) Becker, D. V.; Greenspan, F. S.; Levy, R. P.; Oppenheimer, J. H.; Rivlin, R. S.; Robbins, J.; Vanderlaan, W. P. *JAMA* 237(14): 1459-1460; 1977.

It was recently reported that among patients undergoing mammography at a Detroit hospital, the prevalence of breast cancer was higher in women receiving thyroid hormone therapy than in those who were not. Even if a valid relationship between thyroid hormone therapy and breast cancer had been established, the central question would remain as to whether the cancer is associated with the therapy per se or with the disease for which it was being used. The literature data, although inconclusive, give reason to question the inference that might be drawn from the Detroit study. The American Thyroid Association recommends that patients who are taking thyroid hormones for well-established indications continue to take their medication. Furthermore, the Association recognizes the need for and urges strong support for carefully designed and controlled studies of a possible relationship between the thyroid and breast cancer in humans. (28 refs.)

- 77-0026 Endocrine Status of Women with an Enhanced Risk of Breast Cancer.** (Eng.) Bulbrook, R. D. In: *Breast Cancer: Trends in Research and Treatment. A Monograph of the European Organization for Research on Treatment of Cancer.* Heuson, J. C.; Matthei, W. H.; Rozencweig, M., eds. (New York: Raven Press): pp. 271-277; 1976.

The search for factors that might identify women with an enhanced risk of breast cancer is reviewed. Classic risk factors, such as early menarche or a late first baby, are probably not sufficient. Animal experimental data indicate that endocrine imbalance is an important factor in breast carcinogenesis. Although direct measurements of endocrine status, i.e. estrogens, progesterone, and prolactin, in patients seem to be worth consideration, no striking abnormalities have been found so far in high-risk groups or in patients with breast cancer. Endocrine status appears to be identical in Japanese and British women, but the incidence of breast cancer is considerably higher in the British population. Thus, factors other than hormones must be involved. Although subnormal androgen levels reasonably correlate with risk in Caucasians (leading to a sixfold increase), the reverse is true in Japanese women. Immunological factors may explain these differences. (17 refs.)

- 77-0027 Evaluation of Current Information Concerning the Relationship Between Hormonal Usage and Cancer.** (Eng.) Hertz, R. (George Washington Univ. Sch. Medicine, Washington, DC 20006) *Clin Obstet Gynecol* 20(1): 165-175; 1977.

Data on the relationship between administration of female hormones and cancer are reviewed. The association between vaginal adenocarcinoma and maternal exposure to synthetic

estrogen is statistically highly significant. Three studies have reported increased risk (four to sevenfold of endometrial cancer among users of oral contraceptives. Benign liver tumors, ordinarily extremely rare, have been reported with disturbing frequency in young women using oral contraceptives. There are no firm data on the effects of oral contraceptives on the normal breast. Studies on known carcinogens indicate that 10-20 yr are required for clinical expression of carcinogenicity. (67 refs.)

- 77-0028 Postmenopausal Estrogens and Endometrial Cancer.** (Eng.) Gusberg, S. B. (Dept. Obstetrics and Gynecology, Mount Sinai Sch. Medicine, New York, NY) *CA* 27(1): 47-49; 1977.

Studies indicating increased risk of endometrial cancer in patients using estrogen are reviewed. The risk factor has been reported to be 4.5 for users of any estrogen, 7.5 for users of conjugated estrogens, and 13.9 for those using estrogen for 7 or more yr. It is recommended that women who require estrogen to control flushes or atrophic vaginitis be given estrogen for short periods under medical supervision. Prevention of osteoporosis through diet and exercise rather than estrogen is suggested. (23 refs.)

- 77-0029 Estrogens and Cancer of the Endometrium.** (Eng.) Records, J. W. (Oklahoma City Clinic, 301 NW 12th St., Oklahoma City, OK 73103) *South Med J* 70(1): 1-3; 1977.

The possible increased risk of endometrial cancer in women, associated with the use of estrogen, is discussed. The estimated risk ratio conjugated estrogen users, compared to nonusers, was 7.6% overall and was related to duration of estrogen exposure. The ratio ranged from 5.6% (1-5 yr usage) to 13.9% (over 7 yr usage). Recommendations for the use of estrogen therapy are: use only for severe hot flashes or symptomatic vaginal atrophy; use cyclic administration of the smallest effective dose; if bleeding persists for more than 3 wk after cessation of estrogen, diagnostic procedures should be started immediately. (11 refs.)

- 77-0030 Estrogen Use and Cancer Risk.** (Eng.) Lipsett, M. B. (Clinical Center, Bldg 10, Room IN-212, NIH, Bethesda, MD 20014) *JAMA* 237(11): 1112-1115; 1977.

The relationship between the use of estrogens by postmenopausal women and the occurrence of breast and uterine cancer is reviewed. There is evidence that the risk of cancer increases as the period of estrogen stimulation increases. Three studies showing an increased risk of endometrial cancer among users of estrogens are summarized. The relative risk was found to be 7.6 for users of conjugated estrogens; 4.5 for users of any estrogens was reported from a large (630 women) study, and a risk of 3.3 from a small study. In two of these studies, the risk increased with longer estrogen use.

Increased levels of plasma estrone and estradiol in patients with endometrial cancer have been reported. Conflicting results on breast cancer incidence among users of estrogen have been found; at this time increased risk is not proven. These observations are not considered an indictment of estrogens for postmenopausal women; however, both physician and patient need a clear perception of the risk. (30 refs.)

- 77-0031 New Approaches to the Causation and Prevention of Cancers of Epithelial Surfaces.** (Eng.) Malhotra, S. L. (South Eastern Railway, Calcutta-43, India) *Med Hypotheses* 2(6): 279-281; 1976.

New approaches to the causation and prevention of cancers of epithelial surfaces are discussed. In certain areas of India (Uttar Pradesh) where the incidence of oropharyngeal cancer is high, the betel leaf quids contain a thick layer of slaked lime and are highly alkaline, unlike the acidic quids chewed in other areas. Buccal and pharyngeal malignancies may result from the chronic interaction of this highly alkaline lime on the intracellular mucus of the mucous cells of the epithelium, leading to proliferation, metaplasia, and cell atypia. In other parts of the world, diets deficient in cellulose, vegetable fibers, and roughage produce an alkaline chyme that produces hyperplasia, metaplasia, and chronic inflammatory changes in the colon in the same way as alkaline bile does in the stomach. Also, it has been suggested that it is not the smegma but the increased alkaline pH of the semen that results from frequent sexual intercourse that may bear a causal responsibility for carcinoma of the cervix. Similar considerations apply to the pathogenesis of lung cancer, the risk in smokers with chronic bronchitis being higher than those without the disease, because in chronic bronchitis mucus-bearing goblet cells in the bronchi increase at the expense of the normal ciliated respiratory epithelium. The alkalinity of the cigarette smoke damages these mucous cells, producing metaplasia, cell atypia, and a significant increase in mitotic activity. It is suggested that prolonged contact of the mucus-bearing cells of the epithelial surfaces with an abnormal alkaline milieu should be avoided. (34 refs.)

- 77-0032 Biochemistry of Skin Cancer.** (Eng.) Le Breton, E.; Jacob, A. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumport, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 314-350; 1976.

The biochemistry of skin cancer is reviewed. The application of a carcinogenic polycyclic hydrocarbon to animal skin leads to a process which can be divided into two separate, often independent phases. The first phase is initiation or induction as a result of the penetration and direct contact of the cells with the carcinogenic agent or one of its metabolites. This phase involves the creation of dormant, latent neoplastic cells which are presently indistinguishable from the surrounding normal cells. During the second phase (promotion stage), the dormant cell is transformed into a malignant cell. Once the

transformation of the cancer cell is accomplished, it becomes manifest in two characteristic properties, the result of which is the formation of a malignant tumor: autonomous multiplication and modification of the cell surface. On the histochemical level, malignant transformation is accompanied by collagen destruction following a marked collagenase activity, an alteration of the fibrous structure, and an increase in hyaluronic acid. Moreover, the utilization of energy-producing glucose is increased along with the activity of pentose phosphate shunt. On the nuclear level, covalent linkages between the molecules of carcinogenic hydrocarbons and nucleic acids are accompanied by a depression and subsequent inhibition of macromolecule synthesis. At present, there are three prevalent theories concerning the mechanism of carcinogenesis. The first theory maintains that gene deletions are the determining mechanism. Another theory is based on somatic mutations, ie, modifications of the structural genes. A third theory holds that a number of cancers are caused by anomalies in embryonic development. Studies on the carcinogenic effect of aflatoxin on the rat liver cell are cited as an example of the interaction between nucleic acids and carcinogenesis. (157 refs.)

- 77-0033 Introductory Remarks on AFP Production During Injury and Chemical Carcinogenesis.** (Eng.) Becker, F. F. In: *Onco-Developmental Gene Expression*. Fishman, W.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 207-208; 1976.

The synthesis of α -fetoprotein (AFP) in response to injury and during chemical or spontaneous carcinogenesis is briefly reviewed. AFP is produced in enormous quantities by the fetal liver and is a dominant plasma protein of the in utero period. Adult hepatocytes can resume synthesis of AFP transiently following cell injury or cell division and more persistently following exposure to small quantities of certain hepatocarcinogens. Spontaneous and induced hepatocellular carcinomas of man and animals are capable of synthesizing AFP, occasionally at rates which approach those of the fetal liver. A strong relationship between chromosome composition and AFP production has been demonstrated. Study of AFP control may help in clarifying the role of the fetal phenotype in neoplastic development. (no refs.)

- 77-0034 Summation: Molecular Mechanisms of Gene Regulation--Session 2.** (Eng.) Busch, H. (Dept Pharmacology, Baylor Coll. Medicine, Houston, TX 77030) *Cancer Res* 36(11): 4319; 1976.

One of the major problems in studying the molecular mechanisms of gene regulation has been that of distinguishing events essential to cancer (growth, invasiveness, and metastasis) from the large number of random events that occur in oncogenesis. In this connection, two points are important. One is the randomness of events in carcinogenesis. Chemical carcinogens randomly attack a broad spectrum of cellular products and macromolecules. The result is a range of al-

tered, specialized phenotypes that may exist in tumors of individual organs or even within a tumor mass. Another point is that tumors do not exhibit total randomness. No kidney, heart, intestinal, or other specialized tissue ever arises within a hepatoma mass, despite the variability of these tumors with respect to bile, albumin, and other types of synthesis. Thus, a rigid control exists for phenotype specificity. More information is needed on the nonhistone nuclear protein group, particularly the types of proteins that control genes. There is a lack of evidence for the role of a single protein in this control. Furthermore, the specific roles of phosphorylation and dephosphorylation and other modification reactions have not been clarified. The nature of specific DNA binding and control is very obscure. The accumulation of this information will enable researchers to better comprehend both the dysplasia of cancer cells and the controls of the variable collection of products found in teratomas and teratocarcinomas. (2 refs.)

77-0035 Effect of Carcinogens and Tumor Promoters on Epidermal Cyclic Adenosine 3', 5'-Monophosphate Metabolism. (Eng.) Murray, A. W.; Verma, A. K.; Frosco, M. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 217-229; 1976.

Studies demonstrating the effects of benzo(a)pyrene and tumor promoters on cyclic nucleotide metabolism in the mouse epidermis are summarized. The subjects covered include the effects of benzo(a)pyrene, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), croton oil, and acetic acid on basal cyclic AMP levels and on the hormonal responsiveness of epidermal adenylate cyclase; the effects of benzo(a)pyrene and tumor promoters on epidermal cyclic AMP and cyclic guanosine monophosphate (GMP) phosphodiesterase activities; the relationship between enhanced phosphodiesterase activity and the lack of response to isoproterenol after croton oil treatment; localization of epidermal cyclic AMP by immunofluorescence; and the effect of TPA on epidermal cyclic GMP. It remains to be determined whether the marked changes induced in epidermal cyclic nucleotide metabolism by carcinogens and tumor promoters are related to carcinogenesis. (66 refs.)

77-0036 Progressive Loss of Cellular Metabolic Controls During Hepatic Carcinogenesis. (Eng.) Sabine, J. R. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol. 1, pp. 351-361; 1976.

A new animal model for the study of carcinogenesis is proposed and results from the use of this model are described. The use of hepatoma-prone mice (eg, strains C3H and C3H-A) is recommended; spontaneous hepatomas can occur in 100% of these animals without their being exposed to any

known carcinogenic or toxic agents or situations. In such animals truly carcinogenic changes might be more easily distinguishable from merely toxic events. By using these animals, the early appearance of two control defects that are probably indicative of the tumorous state was determined. These defects, loss of dietary feedback control of cholesterol synthesis and loss of the feedback suppression by heme of the induction of enzyme δ -aminolevulinic acid synthetase (ALAS), were found months before tumors could be found. This model appears useful for the study of cellular control. (36 refs.)

77-0037 Blocking Tumor Production by Protease Inhibitors. (Eng.) Troll, W. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. The Princess Takamatsu Cancer Research Fund. (Tokyo, Japan): pp. 41-55; 1976.

The effect of proteases in tumor promotion by specific agents and hormones and the blocking effects of protease inhibitors are discussed, and several investigations are reviewed. Trypsinlike protease activity in mouse skin was detected 30 min after topical application of the purified principle of croton oil, phorbol-12-myristate-13-acetate (PMA). Protease inhibitors showed the ability to delay tumor promotion and counteract erythema and invasion of leukocytes. The mechanism of action of protease in cancer development is not known. Tumor promoter, as well as hormones, causes phenotypic expression of the genome allowing RNA polymerase to read a new specific portion in chromatin. The action of the protease may be derepression of the genome. Estradiol and estradiol plus progesterone treatments caused the uterus to elaborate a trypsinlike protease in ovariectomized rats. Protease activity was detected in the nuclei of cells from the excised uteri using degradation of histones as the indicator. These studies revealed that the estradiol-induced protease carried out the same histone deletion that was observed by physical separation of the transcribable fraction. This is in agreement with previous findings that specific removal of histones may result in derepression of large regions of the chromatin. (33 refs.)

77-0038 Effects of Protease-Inhibitors of Microbial Origin on Experimental Carcinogenesis. (Eng.) Matsushima, T.; Kakizoe, T.; Kawachi, T.; Hara, K.; Sugimura, T.; Takeuchi, T.; Umezawa, H. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. The Princess Takamatsu Cancer Research Fund. (Tokyo, Japan): pp. 57-69; 1976.

Experiments on the effects of leupeptin on chemical carcinogenesis are reviewed. Leupeptin is a protease inhibitor of microbial origin. Several protease inhibitors have been isolated from culture media of *Actinomycetes*. These inhibitors are potent and highly specific. Leupeptin inhibits trypsin, papain,

lasmin, and cathepsin B. Antipain inhibits trypsin, papain, and cathepsin A and B. Chymostatin inhibits chymotrypsin and cathepsin B. Pepstatin inhibits pepsin, rennin, and cathepsin D. Elastatinal inhibits elastase. In rats, leupeptin suppresses tumor formation in the colon, esophagus, and mammary glands. It has no effect on tumor formation in the forestomach or liver and enhances the growth of tumors in the glandular stomach and urinary bladder. The effects of leupeptin on carcinogenesis vary with species, organs, nature of the carcinogen, and the schedule of carcinogen administration. (17 refs.)

77-0039 Geographic Distribution of Carcinogenic Sun Radiation. (Eng.) Schulze, R. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 172-188; 1976.

Investigations of the dependence of carcinogenic UV radiation on wavelengths showed that the action spectrum for human skin cancer corresponds to the action curve for erythema. Only wavelengths of < 320 nanometers (nm) have a carcinogenic effect, with those equal to 300 nm having a stronger effect than those of 310 or 254 nm. On this basis, radiation dose in biological units was calculated for various geographical latitudes in relation to the seasons. The results show that more than 70% of the carcinogenic radiation is concentrated in the equatorial zone. If industrial pollution causes ozone concentration to decrease by 25%, UV radiation will increase by 40% in the equatorial zone. (37 refs.)

77-0040 A Comment on 'Skin Cancer, Melanoma and Sunlight' (Letter to Editor). (Eng.) Green, A. E. (Dept. Physics and Astronomy, Univ. Florida, Gainesville, FL) *Am J Public Health* 67(1): 59-60; 1977.

Data from three different studies concerning the association of skin cancer incidence with increases in annual UV radiation dose are compared. Differences in differential biological amplification factors, ie UV radiation dose, which were derived in each study for northern, central, and southern locations in the United States are largely attributed to differences in the spectral response function underlying the dose units used in the three studies. One study used doses measured with a Robertson-Berger meter; a second study utilized the Coblentz-Stair erythema response curve as the basis of the dose unit, and a third study used a five-point wavelength rule of response based on an exponential approximation to response curves due to Coblentz and Stair and Urbach and Berger. For the case of non-melanoma skin cancer incidence in particular, all of the studies obtained biological amplification factors substantially greater than the unit factor given in the Report of Federal Interagency Task Force on Inadvertent Modification of the Stratosphere. This report has been the basis of most estimates of the impact of UV radiation increases on skin cancer. (12 refs.)

77-0041 Radiation-Induced Breast Cancer (Letter to Editor). (Eng.) Price, J. L. (Royal Postgraduate Medical Sch., Hammersmith Hosp., London W12, England) *Br Med J* 1(6062): 709-710; 1977.

The risk of carcinogenesis associated with the use of radiation in mammography is discussed. Through improved techniques in recent years, the radiation hazard has been minimized. In London, for the 40- to 50-yr age group, 30.7% of the cancers were found by mammography alone. It is concluded that it would be unfortunate if the possible benefits of screening were denied to this age group before the latest mammography techniques are fully evaluated. (8 refs.)

77-0042 Thorotrast and Tumors of the Liver. (Eng.) Battifora, H. A. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 83-93; 1976.

Approx 120 liver tumors have been attributed to the use of thorotrast. In many cases, the tumors followed large doses (60-80 ml) used for hepatolienography, but in others the patients received smaller doses for arteriography. Essential criteria for a case to be classified as thorotrast-induced is the presence of a tumor in the immediate vicinity of the deposits and a latency period of at least 20 yr. Thorotrast deposits are recognized by a characteristic light microscopic appearance and radioactivity, which is easily demonstrated by autoradiographs of tissue sections. The tumors have the usual histologic spectrum of spontaneous liver neoplasms, but with a disproportionately high number of angiosarcomas. Approx 20% are classified as hepatocellular carcinoma, 32% as cholangiocarcinoma, and 15% as bile duct carcinoma, or histologic combinations of these types. The remaining 33% are predominantly hemangiosarcomas. A case report is given of a 60-yr-old woman who had been hospitalized for a cholecystectomy in 1943. X-ray studies revealed large opaque densities in the liver, spleen, and upper abdominal lymph nodes. She had been given thorotrast at the time of her cholecystectomy. The hepatic architecture was severely distorted. Portal areas were widened by broad bands of connective tissue containing numerous chronic inflammatory cells and histiocytes. One of the biopsies was almost entirely composed of neoplastic tissue. The tumor cells were grouped in anastomosing cords and were slightly larger than normal hepatocytes. The past administration of thorotrast was associated with the development of a mixed hepatocellular carcinoma. (76 refs.)

77-0043 Diversity and Complexity of Carcinogenic Processes: Conceptual Inferences from Foreign-Body Tumorigenesis. (Eng.) Brand, K. G. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455) *J Natl Cancer Inst* 57(5): 973-976; 1976.

Studies of foreign-body (FB) tumorigenesis and of the differences between this process and other types of carcinogenesis are reviewed. Tumorigenesis was initiated by implanting plas-

tic films into CBA/H or CBA/H-T6 mice and then transferring segments of the implants into mice that were histocompatible with the donors, but distinguishable on the basis of the T6 chromosomes. Sarcomas of donor origin developed in the recipients months or years later, indicating that preneoplastic cells were on the FB surface at time of transfer. Tumors that arose from segments of the same original implant were often closely related with regard to latency, chromosome aberrations, histopathology and anaplasia, and growth characteristics in vivo and in vitro. Further studies demonstrated that specific tumor properties were predetermined in pluripotential mesenchymal stem cells of the microvasculature. FB tumorigenesis occurred in four stages, beginning with cellular infiltration by macrophages and ending in a contact-dependent process involving the cell membrane. Since the key event in FB tumorigenesis appears to be intrinsic to the cell, the process differs fundamentally from other types of carcinogenesis in which neoplastic transformation results from direct biomolecular interference or damage by exogenous forces. The FB model is particularly useful for studying the relationship between preneoplastic events and specific tumor characteristics. (20 refs.)

- 77-0044 Malignant Ulcers Following Trauma.** (Eng.) Coburn, R. J. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): Vol. 2, pp. 939-949; 1976.

Marjolin's ulcer, which originally referred to burn scar neoplasia but now is loosely applied to carcinomas originating in scar tissue, is reviewed. The cancer is decreasing in regions where scar management is improving or tribal habits are being abandoned. Males, although less prone to burns and other scar-producing injuries, have three times the incidence of Marjolin's ulcer. Thermal, chemical, electrical, and cold burns produce the vast number of Marjolin's ulcers; within this group the most noxious agent is the thermal burn. Following burns, fistulous tracts, chronic osteomyelitis, and amputation stump, ulcers comprise a far less common second group. A third group is composed of pathologic entities (syphilis, lupus vulgaris, hidradenitis suppurativa, and smallpox vaccinations), following which a small number of patients have been observed to develop neoplasia. The burn scar tumor is generally a carcinoma; the ratio of squamous cells to basal cells is 3:1, but varies with the etiologic agent. Metastasis from scar-associated tumors occurs via the lymphatics in one-third of the patients. The diagnosis of Marjolin's ulcer should be suspected from a history of injury followed by prolonged healing. The therapy of Marjolin's ulcer varies with the three stages of the disease. The premalignant, unstable scar needs wide excision with appropriate soft tissue coverage. Primary treatment of a Marjolin's ulcer confined to the original scar or adjacent tissue is wide surgical excision and skin coverage. Amputation is reserved for deep-seated lesions that extend into bone or joint cavities. The therapy of the end-stage lesions, the metastatic Marjolin's ulcer, usually has poor results, regardless of the approach. A patient's survival

following carcinomatous degeneration of a scar is related to several factors, including (1) microscopic pathology--basal cell lesions almost never metastasize and rarely result in death, and (2) stage at which the lesion is first treated. The prognosis of scar carcinoma in its advanced stage is sufficiently grave to warrant maximum preventive therapy. Since 75 % of such cancers originate after a burn, attention must be focused on improved management of burn scars. (49 refs.)

- 77-0045 Changes in Adenylate Cyclase Activity and Membrane Polypeptides of Cells Transformed with Avian Sarcoma Viruses.** (Eng.) Yoshida, M.; Isaka, T.; Ikawa, Y.; Owada, M.; Toyoshima, K. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 205-215; 1976.

Studies of the effects of avian sarcoma viruses (ASV) on adenylate cyclase activity in chick embryo fibroblasts (CEF) and duck embryo fibroblasts (DEF) are reviewed. All the ASV tested, including B77 and various strains of Rous sarcoma virus, reduced adenylate cyclase activity in transformed CEF; analysis of temperature-sensitive virus mutants showed that the reduction was related to virus-induced transformation. Characteristics of enzyme activity, such as Km, ATP level, and Mg²⁺ and NaF dependence, in the transformed cells showed virus-strain specificity. This virus specificity was confirmed in DEF transformed with the same group of viruses. Changes in adenylate cyclase activity were not correlated with cyclic AMP levels, which were unaffected in transformed CEF but reduced in transformed DEF. The virus-strain specificity observed in the two cell types indicates that changes in the properties of the adenylate cyclase system do not result from induction and functioning of endogenous virus gene but reflect the viral function used for cell transformation. (21 refs.)

- 77-0046 Feline Leukemia Virus. Its Related Diseases and Control.** (Eng.) Hardy, W. D. (Lab. Veterinary Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021) McClelland, A. J. *Vet Clin North Am* 7(1): 93-103; 1977.

Feline leukemia virus (FLV) is an oncogenic RNA virus of the family *Retroviridae*. The virus is spread contagiously among cats living in their natural environment. FLV causes the transformation of lymphoreticular and hematopoietic cells into tumor cells and also causes a number of nonneoplastic diseases in cats. It is an exogenous virus with a smooth outer membrane and a centrally located spherical core containing the genetic material. The fate of an infected cat depends on how it reacts to the virion antigens, the cell surface antigens, and the soluble antigens associated with the oncornaviruses and the cells they infect. Control of the disease calls for the elimination of the infected cat or cats, cleaning the household with ordinary detergents capable of inactivating the virus, and the examination and quarantining of all other

xposed cats. New cats should be tested for feline leukemia virus before entering the household, and only uninfected cats should be used for breeding purposes. There is no evidence that feline leukemia virus can infect humans, but it can be grown in human and canine tissue cultures. (16 refs.)

- 77-0047 **Translation Level Control in Normal and Leukemic Cells.** (Eng.) Hardesty, B.; Kramer, G.; Cimadevilla, M.; Pinphanichakarn, P.; Konecki, D. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): Haematol Bluttransfus Vol. 19, 531-540; 1976.

The translation level control in Friend leukemia cells (FLC) is described. An inhibitory protein present in lysates from uninduced FLC was purified partially by chromatography on DEAE-cellulose and Sephadex G-200. This protein may be responsible for the differential inhibition of globin synthesis observed in a mixed lysate system. This repressor protein does not affect the poly(U)-directed synthesis of polyphenylalanine at a concentration twice as high as that necessary for the max inhibition of reticulocyte messenger RNA (mRNA) translation. It also does not interfere with the completion and release of nascent globin chains initiated in intact reticulocytes. The FLC repressor, however, promotes the protein synthesis dependent breakdown of polysomes in a reticulocyte lysate. The FLC repressor appears to block the initiation of protein synthesis at a point before the sodium fluoride-sensitive reaction of peptide initiation. Ribosomes obtained from reticulocytes incubated with sodium fluoride are almost entirely monomeric, and they seem to be synchronized at a late stage of peptide initiation after attachment to mRNA. The kinetics of polypeptide synthesis in the presence of FLC translational repressor resemble those observed in the presence of edeine. In addition, simultaneous addition of edeine and FLC repressor to the incubation mixture does not result in greater inhibition than that noted with edeine alone. The inhibition of protein synthesis exerted by hemin-controlled repressor (HCR) in reticulocyte lysates may be overcome by an initiation factor that forms a ternary complex. Addition of increasing amounts of a protein fraction, obtained upon fractionation of the rabbit reticulocyte ribosomal salt wash fraction on DEAE-cellulose, that contains the ternary complex formation activity results in the reversal of inhibition exerted by HCR. However, the inhibition produced by the FLC repressor is impervious to increasing amounts of the fraction. A translational repressor is present in lysates from uninduced FLC. (31 refs.)

- 77-0048 **The Murine Sarcoma Virus-Induced Tumor: Exception or General Model in Tumor Immunology?** (Eng.) Levy, J. P. (Laboratoire d'Immunologie des Tumeurs, Service d'Hématologie Groupe INSERM, U 152, Pavillon Gustave Roussy, Hôpital Cochin, Paris, France) *Adv Cancer Res* 24: 1-66; 1977.

The immunological rejection of murine sarcoma virus (MSV)-induced sarcomas, the antiviral immune response, and the antibody and cell-mediated antitumor response are reviewed. The MSV system is interesting because: 1) it is an autochthonous tumor inducing a strong immune response; 2) it can be studied under syngeneic conditions; 3) it has many kinds of surface antigens; and 4) both slow-growing and fast growing sarcomas are produced. (262 refs.)

- 77-0049 **Selective Techniques for the Isolation of Morphological Revertants of Sarcoma Virus-Transformed Cells.** (Eng.) Greenberger, J. S. (Joint Center Radiation Therapy, Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA) Bensinger, W. I.; Aaronson, S. A. *Methods Cell Biol* XIV: 237-249; 1976.

Morphological revertants of sarcoma virus-transformed cells were isolated by techniques based on methods used to increase the frequency of isolation of conditioned lethal mutants of avian sarcoma virus. Single cells were suspended in semisolid medium containing agar or methyl cellulose, which allowed only the transformed cells to replicate. An antimetabolite was then added to the culture. After an appropriate time interval, the surviving cells were removed from the suspension, washed free of the antimetabolite, and plated for subsequent selection of normal-appearing cells. The effects of varying concentrations of cytotoxic drugs (iododeoxyuridine, 5-fluorouracil, and ³H-thymidine) on the colony-forming efficiency of the virus-transformed cells were compared to the control BALB/3T3 line. The optimum concentration of each drug gave a ten- to hundredfold selective kill of the transformed cells. Both the in vitro and in vivo biological properties of morphological revertants were indistinguishable from those of the control BALB/3T3 cell line and very different from those of the malignant sarcoma virus-transformed line, from which each was isolated. The murine sarcoma virus-transformed nonproducer cell revertants should be of use in developing a better understanding of the virus-cell interactions involved in transformation. (1 refs.)

- 77-0050 **Biochemical Characterization of Mouse Mammary Tumor Viruses and Related Isolates: Mason-Pfizer Virus and the BUdR-Induced Guinea Pig Virus.** (Eng.) Schlom, J.; Colcher, D.; Drohan, W.; Kimball, P.; Michalides, R.; Schochetman, G. In: *Breast Cancer: Trends in Research and Treatment. A Monograph of the European Organization for Research on Treatment of Cancer*. Heuson, J. C.; Matthei, W. H.; Rozenzweig, M., eds. (New York: Raven Press Books, Ltd.): pp. 11-56; 1976.

The characteristics of mouse mammary tumor viruses (MMTV) and two related isolates, Mason-Pfizer virus (MPV) and bromodeoxyuridine (BUdR)-induced guinea pig virus (B-GPV), are reviewed and compared. The intracytoplasmic A particle, which may be a precursor of the type B particle, has been observed regularly in cells producing MMTV. Radioimmunoassays have been used to quantitate and character-

ize variant MMTV's being produced from RIII, GR, DD, BALB/cC3H, and BALB/c mammary tumor cultures. Virions produced in culture possess the density, sedimentation properties, RNA, and reverse transcriptase activity of MMTV's obtained from mouse milk. Generally, the av primary culture produced approximately 5×10^{10} MMTV particles/day/75 cm² flask. No common nucleic acid sequences were detected between the RNA's of MMTV's and those of murine leukemia virus (MuLV)-Rauscher, B-GPV, or MPV. The viral genome of the horizontally transmitted variants from GR, RIII, C3H, and A mice was at least 95% homologous, as analyzed by molecular competitive hybridization, and about 25% different from the vertically transmitted variant from C3H-AvyfB mice. The six distinct polypeptides found to be associated with MPV (which was isolated from a rhesus monkey breast carcinoma) may be virus-coded and not derived from host cell components. The similarities of the RNA structure of MPV and B-GPV to that of other oncornaviruses are elucidated. No detectable nucleic acid sequence homology was observed between MPV 60S-70S RNA and the RNA's of types B and C viruses. MPV does not appear to be an endogenous virus of humans. B-GPV is similar to the B-type MMTV in many stages of morphogenesis and appears to be a true endogenous virus. Although there is a lack of detectable sequence homology among B-GPV, MPV, and MMTV, these viruses share several structural and biochemical properties, including a Mg^{++} cation preference, and they appear to be relatively free of type C particles. (103 refs.)

- 77-0051 **Viro-immunology in Breast Cancer.** (Eng.) Humphrey, L. J. (No affiliation given) *Breast* 2(4): 31-33; 1976.

Recognition of the role of a virus in the etiology of breast carcinoma goes back several decades to the discovery of the Bittner agent or milk factor. Sufficient data have since demonstrated that the milk factor is a mammary tumor virus. The work of Duran-Reynals on chronic irritation has been applied to the breast. Chronic irritation, with its inflammatory response, occurs in the human breast in a manner that is mechanistically similar to the Duran-Reynals model. However, the existence of a chronic inflammatory response and the implication of a virus similar to murine mammary tumor virus do not constitute proof that human breast cancer is caused wholly or in part by an oncogenic agent. Isolation of the virus from breast cancer tissue and appropriately controlled transformation of normal breast cells to malignant cells would offer convincing evidence. Tumor-associated antigens or antibodies and other immune phenomena have been described, but documentation of breast-cancer-specific antigens and antibodies is still lacking. There is evidence that autoimmune phenomena are associated with breast cancer. Two autoantibodies have been described: one is directed against the Fc of immunoglobulin; the second is an autoantibody directed against the antigen-binding fragment of immunoglobulin. The sera from breast cancer patients and from those with fibroadenoma do react against antigens in breast cancer tissue. (27 refs.)

- 77-0052 **Herpes Simplex Virus and Carcinoma of the Cervix.** (Eng.) Thiry, L. (Institut Pasteur du Brabant, Bruxelles, Belgium) *Europ J Cancer* 12(11): 851-858; 1976.

Some hypotheses relating to herpes simplex type 2 virus (HSV-2) are reviewed. Studies with hamsters and cebus monkeys have indicated that HSV-2 infection is associated with increased incidence of neoplasms. DNA from HSV representing 39% of the viral genome was demonstrated in one cervical carcinoma. Protein Ag 4 has been isolated from human cervical carcinoma cells and used as an antigen. A positive reaction was found in 90% of patients with invasive cervical carcinoma vs 10% of matched controls. Negative reactions were found in successfully treated patients and positive reactions in those with recurrence. Antibodies to cytomegalovirus and Epstein-Barr virus have been found in increased incidence in women with cervical cancer, but information from these viruses has not been demonstrated in cancer cells. (55 refs.)

- 77-0053 **Viral Etiology of Lymphoma and Leukemia in Humans.** (Ger.) Bauer, H. (Institut für Virologie, Bereich Humanmedizin, Justus-Liebig-Universität Giessen, Giessen, W. Germany) *Haematol Bluttransfus* 18: 1-15; 1976.

Studies of the virus etiology of lymphomas and leukemias in humans are reviewed. So far, only Epstein-Barr virus has been identified as an etiological agent of human tumors, and only in Burkitt's lymphoma and nasopharyngeal tumor in Africa. Tumor was induced in monkeys with a virus isolated from infectious mononucleosis, which suggests the similarity of the Epstein-Barr and infectious mononucleosis viruses. An enzyme was isolated exclusively from human leukemia cells that appears to be oncornavirus-specific. It has proved to be immunologically similar to the reverse transcriptase of C-type avian viruses. An oncornavirus was isolated from these cells, but contamination with an avian virus cannot yet be ruled out. An oncornavirus was also isolated from human lymphosarcomas, and oncornaviruslike particles were recently isolated from human fibroblast cell lines. It has been found possible to immunize mice to tumor cells with tumor specific cell surface antigens from syngeneic mice. (22 refs.)

- 77-0054 **Transformation-Defective Mutants of Polyoma Virus.** (Eng.) Benjamin, T. L. In: *Oncogenes: Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 85-87; 1976.

The discovery of mutants of a viral gene that have a restricted host range (hr) and are unable to induce neoplastic transformation (-t) is reported. Nineteen of these hr-t mutants have been isolated from polyoma-transformed 3T3 cells. The mu-

ants were derived from NG-18 and were unable to induce cell surface alteration characteristic of transformed cells; this may underlie their inability to cause neoplastic transformation. These mutants were subsequently grown on C-type RNA virally infected 3T3 cells and on primary mouse embryo fibroblasts. Marker experiments indicated that a single wild type viral DNA restriction enzyme fragment can restore both a normal host range and the transformation ability of the mutants. Hr-t mutants, as well as particles of wild-type virus, contain histones derived from the cell. Histones H-3 and H-4, derived from the wild type, showed more extensive acetylation than normal host cell chromatin, while the same two histone fractions from mutant particles showed little increase in acetylation over the host. (11 refs.)

- 77-0055 **New Topics in Infectious Medicine.** (Ger.) Mayr, A. (Institut für Medizinische Mikrobiologie, Infektions- und Seuchenmedizin, Fachbereich Tiermedizin, Ludwig-Maximilians-Universität, D-8000 Munich 22, Veterinarstr. 13, W. Germany) *Zentralbl Bakteriol [Orig B]* 63(1/4): 81-95; 1976.

New problems of infectious medicine are reviewed. Certain viruses, mainly DNA viruses such as papovavirus, adenovirus, herpesvirus, and smallpox virus, transform cells to malignant ones only when special combinations of certain factors are present. Otherwise, they cause ordinary viral infections and diseases. Another group of viruses, oncornaviruses, which are mainly RNA viruses, are specifically oncogenic in reptiles, rodents, birds, cattle, sheep, cats, dogs, monkeys, and humans. The cellular DNA of vertebrates contains a segment that corresponds exactly to the sequence of the C-type RNA virus genome. Noninfected cells release C-type RNA viruses after treatment with certain inducing agents, eg, halogenated pyrimidines. Free murine embryonal cells and cells from adults with an increased cell proliferation rate have high titers of group-specific C-type RNA virus antigen, but nonproliferating tissues are nearly free from this antigen. If the DNA segments corresponding to the sequence of the C-type genome were indeed responsible for cell proliferation, this would confirm the endogenous genesis of tumor viruses. Thus, carcinogenesis would result from the interaction of an exogenous agent and an endogenous tumor virus genome. (28 refs.)

- 77-0056 **Proteolytic Cleavage Events in Oncornavirus Protein Synthesis.** (Eng.) Shapiro, S. Z. (Dept. Molecular Biology, Albert Einstein Coll. Medicine, Bronx, NY 10461) *Biochim Biophys Acta* 458(4): 375-396; 1976.

Proteolytic cleavage in oncornavirus protein synthesis is reviewed. Categories of virus protein proteolytic cleavages are discussed in terms of virus particle morphogenesis, virus protein activation, and cleavage of very large "polyproteins" during virus production. Cleavage of the polyproteins is discussed in terms of picornaviruses and α togaviruses. Type C oncornavirus precursor proteins includes a discussion of avi-

an oncornavirus protein synthesis and cleavage, mammalian oncornavirus protein synthesis and cleavage, and studies of translation of oncornaviral RNA. Virus protein precursor cleavage enzymes are also discussed, and models of oncornavirus protein synthesis and virus genetic structure are presented. (135 refs.)

- 77-0057 **Endogenous Type-C RNA Viruses of Mammalian Cells.** (Eng.) Aaronson, S. A. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014) *Biochim Biophys Acta* 458(4): 323-354; 1976.

Endogenous viruses exist in species as diverse as the chicken, mouse, and baboon, and there is evidence suggesting their presence within some species over a long period of evolution. In this review the known properties of mammalian C-type viruses are described, and experimental evidence of their genetic transmission is summarized; mammalian sarcoma viruses and helper or helper-leukemia viruses are covered. Data on the known distribution of endogenous viruses among mammalian species and evidence concerning the regulation of their expression by the host are presented. Finally, some of the possible biologic functions of the virus are discussed, including cellular differentiation, transduction of genetic information, neoplastic transformation, and immunosurveillance. (250 refs.)

- 77-0058 **Endogenous Type-C RNA Viruses of Mouse Cells: A Model for the Study of Gene Regulation in Eukaryotes.** (Eng.) Aaronson, S. A.; Stephenson, J. R.; Hino, S.; Cabradilla, C. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 279-294; 1976.

Current knowledge concerning the biologic regulation of endogenous C-type viral genes and some of their possible functions is discussed. The specific topics covered include the properties of three biologically distinguishable viruses isolated from BALB/c and NIH mice; the differential activation of the three viruses; mechanisms of C-type virus activation by halogenated pyrimidines and inhibitors of protein synthesis; enhancement of virus release by steroid hormones; the genetic control of endogenous virus activation; the release of C-type viruses from lymphoid cells after antigenic stimulation; and the possible role of viruses in tumor rejection, cell differentiation, and information transfer. (62 refs.)

- 77-0059 **RNA Tumor Viruses and Leukemia: Evaluation of Present Results Supporting their Presence in Human Leukemias.** (Eng.) Gallo, R. C. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutic and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp.431-450; 1976.

Evidence supporting the presence of type-C RNA viruses in human leukemias is reviewed. Although human myelogenous leukemia blood cells do not frequently permit complete expression of type-C viral information, this information is apparently at least partially present in many and perhaps all acute myelogenous leukemia (AML) patients. Cells from several leukemia patients have expressed readily detectable viral markers (proteins and/or nucleic acids) specifically related to simian sarcoma virus (SSV). Cells from one AML patient released a classical budding type-C virus. The fresh blood cells from this patient contained reverse transcriptase related to SSV; it was possible to reisolate the virus from the same patient. Type-C viruses related to or identical with SSV have also been isolated twice from a child with lymphosarcoma leukemia. Recently, a DNA provirus was identified in humans for the first time. The provirus of a virus highly related to or identical with baboon endogenous type-C virus was found in the DNA of uncultured tissues from several but not all leukemia patients. These results demonstrate that humans are infected by type-C virus and suggest an interspecies transfer of virus from baboon to man in the past. A major component of the repeated isolates of HL23 virus from a patient with AML were highly related to the baboon endogenous type-C virus; these isolates appear to be from the patient and not from laboratory contamination. It is possible, though not proven, that this acquired viral information is causatively involved in leukemia. (57 refs.)

- 77-0060 In Vitro Interactions Between Tumor Cells and Immune Lymphoid Cells.** (Eng.) Levy, J. P. (No affiliation given) Gomard, E.; Senik, A.; Leclerc, J. C. *Recent Results Cancer Res* 56: 24-30; 1976.

When tumor and immune lymphoid cells are mixed in vitro, several different phenomena occur simultaneously that cannot be separated by the microcytotoxicity assay, but they can be analyzed easily by more precise methods. Aliquots of the same lymphoid and target cell mixtures were investigated by the chromium release test (CRT), the cytostasis assay, and the secondary CRT (S.CRT), which permits the secondary antitumor response to be measured, with in vitro activation of the cytolytic T lymphocytes. The experimental conditions were the same in all three tests, except that the CRT was determined during the first few hours by adding chromium-labeled target cells at the start of the incubation period, the S.CRT was determined by adding identical target cells in the coculture on day 3, and the cytostasis assay was determined at the same time by measuring ^3H -thymidine incorporation in the 3-day cocultivated tumor cells. On day 1, a significant T lymphocyte-mediated cytotoxicity occurred because of the cytolytic T lymphocytes already present in vivo in the donor mice. All the target cells were not destroyed, and after 2 days a population relatively resistant to the immune cytotoxicity was selected. Tumor cells in vitro stimulated the T cells to maintain and even significantly increase the cytolytic T lymphocyte activity of the whole culture. On the other hand, in the absence of stimulating tumor cells, the cytolytic T lymphocyte activity rapidly decreased. During incubation,

non-T cells, which are mainly macrophages, were activated by the interaction of immune lymphoid cells and tumor cells, but the activation is nonspecific. The comparison of different methods may make it possible to determine the different target antigens in the cell-mediated immune reactions observed in vitro and to compare these reactions with in vivo tumor rejection. (30 refs.)

- 77-0061 Molecular Evidence for the Association of RNA Tumor Viruses with Human Mesenchymal Malignancies.** (Eng.) Spiegelman, S. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutic and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 391-429; 1976.

Molecular evidence for an association between RNA tumor viruses and human malignancies is reviewed. Nucleic acid hybridization and other techniques of molecular biology have demonstrated that human neoplasias contain RNA molecules possessing detectable homologies to the RNA of tumor viruses which cause similar cancers in animal systems. The RNA molecules identified in human tumors have the size and physical association with reverse transcriptase that characterizes the RNA of animal oncornaviruses. The tumor-specific RNA is encapsulated in a particle the size and density of the RNA tumor viruses. Viral-related sequences are unique to the DNA of tumor cells and are inserted postzygotically; they are therefore not resident in the germ line. Particles with diagnostic criteria associated with oncornavirus-like particles found in mesenchymal tumors have no sequences in common with those in breast cancer. These differences appear to extend to the particles found in other sorts of primary tumors. These results suggest the possibility of developing a novel pathway for specific tumor detection. (72 refs.)

- 77-0062 Tumor Immunity.** (Eng.) Sanford, B. (Bethesda, MD) McKhann, C. F. *Transplant Proc* 9(1): 1307-1309; 1977.

The specificity of immune reactions to tumor cells, suppression of immunity and escape mechanisms, and immunotherapy are summarized briefly by citations of individual research. Data are given on the nonspecific cytotoxicity of lymphocytes from 10 normal donors against three cultured lines of tumor cells. In another study, the lymphocytes from an extensive series of melanoma patients were tested on target cells at ratios ranging from 50:1 to 1,000:1. No significant cytotoxicity in excess of the relatively high levels observed in normal controls was found. Concerning suppression of immunity and escape mechanisms, the question was raised of why small numbers of some tumor cells are able to kill the host. Evidence is presented that the tumor cells themselves may undergo antigenic modulation while growing in the host. A study was made of the use of neuraminidase-treated tumor cells in the immunotherapy of mammary carcinoma in dogs. (no refs.)

- 77-0063 **The Cancer Connection.** (Eng.) Anonymous (No affiliation given) *Lancet* 1(8012): 635-636; 1977.

The host immunological response to contact with cancer is a phenomenon that is not yet totally understood. Increased tumor sensitization has been reported in persons who are in close contact with patients with leukemias, Burkitt's lymphoma, breast cancer, and various sarcomas. Studies of sensitization of cage contacts of animals with tumors induced by infective and noninfective carcinogenic agents should produce more evidence. The total incidence of disease in cancer contacts must be examined over a long period of time. (15 refs.)

- 77-0064 **Immune Defense, T-Cell Immunosuppression, and Cancer.** (Spa.) Rodriguez Paradisi, E. Laboratorio de Immunogenetica, Instituto de Oncologia "Angel H. Roffo", Universidad de Buenos Aires, Buenos Aires, Argentina) *Sangre* 21(3): 523-528; 1976.

Data contradicting the assumption that the T-cell system is an immune defense against cancer and that it weakens with age are presented briefly. The frequency of spontaneous tumors is the same in thymectomized and control rats. Aging NZB/BL rats implanted with syngeneic tumors have a smaller percentage of tumors than young controls. Nude rats, which have congenital aplasia of the thymus and auxiliary functional system, do not display an increase in nonlymphatic tumors. Human congenital immune deficiencies can be accompanied by lymphomas or malignant tumors of the hematopoietic system but not by other types of tumors from nonlymphatic tissue. Therapeutic immunosuppression is frequently followed by the appearance of lymphomas and other tumors of probable viral origin. The direct cytotoxic reaction of lymphocytes against syngeneic tumor cells is sometimes greater when the lymphocytes come from the lymph nodes of a "B rat" rather than from normal lymph nodes. Spontaneous tumors occur with equal frequency with a progressive increase or decrease in the buildup of a persistent and effective defense. (49 refs.)

- 77-0065 **Side Effects and Possible Harmful Action of Immunomanipulation.** (Eng.) Mathe, G. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology. Meeting held at Montpellier, June 1975.* (New York: American Elsevier Publishing Co.): Vol. 17, pp. 67-82; 1976.

Immunodepression may be induced deliberately, as in cases of allogeneic transplantation; however, it is a side effect of some cancer therapy that is to be avoided. Serious infections may result from the continued use of cytostatic drugs and/or radiotherapy in cancer patients. Intermittent, even intensive chemotherapy has been reported to be less immunosuppressive than continuous daily chemotherapy at small doses. Tumorigenesis may also result from immunosuppression due to transplantation. Many of the tumors in immunosuppressed

patients are known as immunoblastic lymphosarcomas, the result of mutation induced by a virus or by the antigen-induced proliferation of reacting lymphocytes. (91 refs.)

- 77-0066 **Malignant Tumors in Patients Treated with Immunosuppressive Agents.** (Eng.) Wegman, W. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology. Meeting held at Montpellier, June 1975.* (New York: American Elsevier Publishing Co.): Vol. 17, pp. 95-99; 1976.

In a series of 204 renal transplant patients who survived kidney transplantation for > 4 mo, 4 developed malignant lymphoma and 1 developed bladder carcinoma, a 3% tumor incidence. The pathogenesis of cancer in the posttransplant period may be due to several factors, including loss of host immunosurveillance, reactivation of oncogenic viruses, and chronic immunostimulation. However, if a defect in the immunosurveillance system were the cause of tumorigenesis, a broad spectrum of tumors would be expected, which does not explain why in this series 80% of the tumors were malignant lymphomas. (34 refs.)

- 77-0067 **Introductory Remarks on Gene Expression in Development.** (Eng.) Engo, Y. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 93-94; 1976.

The synthesis of α -fetoprotein (AFP) in mammalian fetuses occurs mainly in the liver and yolk sac, and to a very small extent, in the gastrointestinal tract. This finding explains the reappearance of AFP in primary liver cancer, yolk sac tumor, and a few cases of gastric carcinoma. As many as 60% of the patients with teratocarcinomas have been found to have abnormally high levels of serum AFP. AFP determination is valuable in the differential diagnosis of benign and malignant teratoma. In cases of yolk sac tumors, it reflects the progress of the illness and the effect of the treatment. However, the mechanisms and location of AFP synthesis in teratocarcinomas and other tumors remain unknown. Little is known about the biologic function of AFP but recent investigations on estrogen-binding ability and the immunosuppressive activity of AFP shed some light on this problem. (no refs.)

- 77-0068 **Introductory Remarks on Physiology, Metabolism, and Immune Effects of Onco-Developmental Gene Products.** (Eng.) Uriel, J. In: *Onco-Developmental Gene Expression.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): p. 285; 1976.

The biological properties of α -fetoprotein (AFP) are briefly discussed. It is known that mouse and rat AFP are estrogen

binders of high affinity and that amniotic fluid and other fetal fluids from several mammalian species are immunosuppressive. Estrogen-binding ability may be a general property of AFP or a property restricted to AFP from rodents. There is evidence that the estrogen-binding capacity of AFP in serum and other biological fluids differs greatly from one species to another, probably because there are variable proportions of two molecular populations of AFP, only one of which possesses embryonic properties. The possible immunosuppressive activity of AFP is of critical interest. (no refs.)

- 77-0069 **Immunogenicity of Tumor Antigens.** (Eng.) Herberman, R. B. In: *Immunocancerology in Solid Tumors*. Martin, M.; Dionne, L., eds. (Miami: Symposia Specialists): pp. 3-14; 1976.

The rationale for studying more than one tumor system as models for clinical tumor immunology is that each one has its own peculiarities. By looking for common factors in several models, one can derive the general principles that are likely to be applicable to the clinical situation. The (C58NT)D tumor, a Gross virus-induced lymphoma in W/Fu rats, and the FBL-3 tumor (a Friend virus-induced lymphoma in C57BL/6 mice) are two highly immunogenic models that produce strong resistance against tumor challenge. The murine sarcoma virus-induced tumor is perhaps the most popular tumor model being used to study host resistance against tumor growth. In each of the tumor systems, if the animals are not rechallenged, there are negligible levels of cytotoxicity after the initial response. However, if they are rechallenged with tumor cells, within 2-3 days there is a very rapid response, with generation of cytotoxic cells. This response occurs predominantly in the region of challenge. Similarly, in vitro, without antigenic stimulation, low levels of cytotoxicity are detectable, whereas reexposure of the memory cells to the antigen results in high cytotoxicity levels within approx 4-6 days. Sera from tumor-bearing rats can block the proliferative response to tumor antigens, whereas normal rat sera or sera from animals whose tumors have regressed do not have a blocking effect. There is considerable complexity in the detectable immune responses. (no refs.)

- 77-0070 **Assessment of Cell-Mediated Immunity to Human Tumor-Associated Antigens.** (Eng.) Baldwin, R. W. (Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, England) Embleton, M. J. *Int Rev Exp Pathol* 17: 49-95; 1977.

Cell-mediated immunity to human tumor-associated antigens is reviewed. Immunity to human tumors has been demonstrated by various in vitro techniques including colony inhibition, microcytotoxicity, ^{51}Cr -release cytotoxicity, leukocyte migration or adherence inhibition, and lymphocyte stimulation by inactivated tumor cells or extracts. Serologic tests to detect human tumor associated antigens reveal conflicting data in malignant melanoma. Some studies reveal high tumor-related antibody activity in patients' sera and low reactivity in nor-

mal subjects, and other studies show higher activity in normal sera. Humoral factors may interfere with cell-mediated immunity in human cancer. This interference may be caused by an interaction of tumor-specific antibody, or by immune complexes with neoantigens preventing recognition by sensitized lymphoid cells, or by inhibition of effector cell reactivity by direct interaction of serum-born tumor antigen or immune complexes. Cytotoxicity tests indicate a tissue-related specificity of reactions by cancer patients above a background level of normal reactivity. Cell-mediated immune response to tumor-associated products was demonstrated using delayed hypersensitivity skin testing in patients with breast cancer, carcinoma of the colon, lung cancer, melanoma, leukemia, and Burkitt's lymphoma. Evidence derived from in vitro assays supports the concept that human tumors express neoantigens similar to those detected on experimental tumors. (180 refs.)

- 77-0071 **Anergy, Anti-Antibodies and Immune Complex Disease: A Syndrome of Disordered Immune Regulation in Human Cancer.** (Eng.) Jerry, L. M.; Lewis, M. G.; Cano, P. In: *Immunocancerology in Solid Tumors*. Martin, M.; Dionne, L., eds. (Miami: Symposia Specialists): pp. 63-79; 1976.

Lymphocyte cytotoxicity in melanoma patients tends to demonstrate a stage relationship, being higher when the tumor is localized and falling with advancing disease. Although cytotoxicity disappears in advanced disease, it can be readily resurrected by specific or nonspecific immunotherapy. Low levels are observed against normal fetal cells and unrelated tumors such as ovarian carcinoma. Sera from 37 melanoma patients were tested for the presence of rheumatoid factorlike anti- γ -globulins by standard latex agglutination and by radial diffusion into agarose plates containing aggregated human immunoglobulin G. Anti- γ -globulins were found in 10/37 patients, particularly those with advancing tumor stage. There is growing evidence for immune complex-mediated phenomena in a variety of human and animal tumors, including melanoma. The sera of some cancer patients contain blocking factors that can prevent their own sensitized lymphocytes from attacking autologous tumor cells; they have been identified as soluble immune complexes, antitumor antibodies, or soluble tumor antigens. In addition to cancer, one or more of the phenomena of anergy, antiantibodies, and immune complexes have been found in several disorders, especially chronic infections, chronic parasitic disease, and rheumatic disorders. When the sera from 56 melanoma patients were examined, increased levels of immune complexes tended to appear with advancing disease. The object of immunotherapy should be to restore disordered immune regulation. (31 refs.)

- 77-0072 **Tumor-Associated Immunoglobulins vs. Immune Surveillance.** (Eng.) Dorval, G. In: *Immunocancerology in Solid Tumors*. Martin, M.; Dionne, L., eds. (Miami: Symposia Specialists): pp. 15-25; 1976.

The fixation of immunoglobulins (Ig) increases with tumor age after inoculation in vivo, reaching a plateau during the preterminal days of the tumor-bearer. Conversely, it decreases rapidly after explantation of the tumor to in vitro metabolic conditions. Tumor-bound Ig contains antibodies directed against specific neoantigens expressed on the tumor cells themselves. Blastogenesis of lymphocytes has been correlated with detectable Ig content in autologous human cancer biopsies: tumors that fixed Ig in vivo were not stimulatory for autologous lymphocytes, whereas 46% of biopsies with a low or undetectable Ig "coat" were stimulatory. When murine tumors are inoculated in vivo with an acid eluate prepared from the corresponding tumor, there is a significantly higher incidence of tumors in test animals than in control groups inoculated with tumor cells alone or admixed with an acid eluate from another tumor. This growth-enhancing effect is attributed to the IgG₂ content of the acid tumor eluate. The immune response is actually associated with progression of tumor growth. During the early phase of relatively low neoplastic burden, specific immune parameters, cellular or humoral, are observed. That the cellular components disappear or that the cellular effectors are blocked during the later phase of disseminated disease may be only partly relevant to the actual role of immunity in tumor resistance. Numerous observations have been made in vivo and in vitro on immune-induced facilitation of tumor growth, leading to the concept of countersurveillance. A composite immune and nonimmune interaction pattern is involved in tumor growth, and already "grown-up" tumors may not be totally relevant to the surveillance doctrine per se. (98 refs.)

77-0073 Blocking and Unblocking Serum Factors in Neoplasia. (Eng.) Bansal, S. C. (Dept. Surgery, Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA 19129) Bansal, B. R.; Boland, J. P. *Curr Top Microbiol Immunol* 75: 45-76; 1976.

The various factors involved in the performance of a microcytotoxicity assay may cause different results, resulting in confusion as to their possible meaning. It is complex and far from an ideal technique for routine usage to evaluate antitumor immune response in all types of tumor-host relationships. Nevertheless, in a syngeneic tumor model and under controlled conditions, the in vitro data obtained do reflect the tumor status in vivo. Blocking serum activity, as measured in vitro, is related to the degree of effective host response to the tumor in vivo. A significant correlation between the blocking serum activity in vitro and tumor growth in vivo has been obtained by serial analysis of the tumor-host relationship. The specificity of the blocking phenomenon indicates that the cytotoxic effect of lymphocytes is directed against tumor-related antigens rather than normal alloantigens. Blocking factors may play an important role in tumor growth and their removal or inhibition of production may be beneficial to the host. Certain antitumor immune sera can abrogate the blocking activities of sera and tumor eluates from tumor-bearing individuals when admixed in vitro. Unblocking serum always exerts a cytotoxic effect on target cells in vitro in the presence of complement. In tumor-bearing in-

dividuals, there is a balance between free-tumor antigen, antigen-antibody complexes of various sizes and types, and different types of antitumor antibodies having different biological functions. In different tumor-host situations, this balance may be shifted, depending upon the antigen-shedding capacity of the tumor cells, synthesis, and metabolism of antitumor antibodies and their complexes by the host. The practical problems of in vitro analysis of antitumor immune response and immunologic intervention are complex, because the tumor-host relationship is poorly understood. (125 refs.)

77-0074 Immunological Aspects of Inflammatory Granulomas. (Fre.) Nezelof, C. (Groupe de Pathologie Pédiatrique, INSERM (U77), Necker-Enfants Malades, 149, rue de Sevres, 75730 Paris Cedex 15, France) Vilde, F. *Arch Anat Cytol Pathol* 24(6): 431-457; 1976.

Studies on the immunological aspects of acute and chronic inflammatory granulomas are reviewed. Chronic granuloma, which indicates the failure of conventional immunological and inflammatory reactions to eliminate the antigens, may be due to the refractory character of the causative agent, to the permanent renewal of antigen sources (such as in autoimmune diseases and circulating immune complexes), to hypersensitivity to a specific antigen, and to immune deficiency affecting opsonization, eg, immune deficiency due to cancer. (180 refs.)

77-0075 Immunochemical and Immunocytological Findings in Non-Hodgkin Lymphomas. (Ger.) Stein, H. (Pathologisches Institut, Universität Kiel, Kiel, W. Germany) *Haematol Bluttransfus* 18: 167-183; 1976.

Immunological findings in non-Hodgkin lymphomas according to the Kiel classification are presented. Centroblastic/centrocytic lymphoma contains nonsecreting cells; the serum immunoglobulin (Ig) level is almost always reduced or normal. Most tumor cells carry membrane Ig. Similar findings were obtained for centrocytic lymphoma (centrocytoma); complement receptor (CR) was found in all cases. The centroblastic lymphomas (centroblastomas) investigated exhibited the criteria of B-cell lymphoma. The recent detection of CRs on cells of European Burkitt's lymphoma (lymphoma morphologically resembling Burkitt's lymphoma but without the Epstein-Barr virus genome) may justify the classification of this tumor as a germinal center cell tumor. Two types of Ig-positive immunoblastic sarcomas were distinguished immunologically: (1) a CR-negative sarcoma originating possibly from immunoblasts of the plasma cell reaction, and (2) a CR-positive sarcoma originating from immunoblasts of the germinal center reaction. Ig production was observed in almost all cases of chronic lymphocytic leukemia (CLL) and lymphoplasmacytoid lymphoma (immunocytoma). Immunologically, classical B-cell CLL is defined as an irreversible proliferation of nonsecreting, Ig-producing lymphocytoid cells, whose maturation and transformation to secreting Ig-forming cells are blocked. The maturation may take place in

isolated cases, leading to immunocytoma. The CLL may originate from virgin B1 lymphocytes from the bone marrow and/or from circulating B2 lymphocytes from the germinal center reaction. Lymphoblastic lymphoma with acid phosphatase reactivity most likely is a neoplasia of T-precursor cells. The acid phosphatase-negative convoluted cell-type lymphoma may originate from late fetal thymocytes or post-natal thymocytes. (24 refs.)

77-0076 Immunology: Breast Cancer. (Eng.) Heppner, G. H. (Div. Biological and Medical Sciences, Brown Univ., Providence, RI 02908) *Rec Results Cancer Res* 57: 95-108; 1976.

The evidence for immune reactivity to human breast cancer is summarized. Antibodies reacting with mouse mammary tumor virus (MTV) have been detected in the sera of some women with breast cancer by several techniques. The migration of WBC from about 30% of breast cancer patients is inhibited by MTV but not by virus-free mouse milk. This WBC reactivity was found in only 5% of patients under 45 yr old, but in 39% of WBC from older patients. Invasive breast carcinomas are less antigenic than in situ disease. Breast cancer patients are generally immunocompetent. (48 refs.)

77-0077 Chromosomal Abnormalities and Their Specificity in Human Neoplasms: An Assessment of Recent Observations by Banding Techniques. (Eng.) Mark, J. (Dept. Pathology, Central Hosp., 541 01 Skoevde, Sweden) *Adv Cancer Res* 24: 165-222; 1977.

The cytogenetic observations of three groups of neoplastic or preneoplastic conditions (meningiomas, myeloproliferative, and lymphoproliferative disorders) are reviewed. The data indicate that some autosomal chromosomes, eg 1, 8, 14 and 22, are involved more frequently than others in the deviations of neoplastic conditions. There are indications that the variations among the autosome in different neoplasms have common features. For instance, a 9q+ marker has been found in Ph⁺-positive chronic myelocytic leukemia, in a lymphosarcoma cell line, and in a meningioma. (245 refs.)

77-0078 Genetics and Cancer. (Eng.) Cox, R. P. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 137-162; 1976.

Genetic components involved in the etiology of cancer are discussed, with particular reference to skin cancer. Cancerous diseases showing a clear-cut genetic basis in terms of Mendelian inheritance include: xeroderma pigmentation, multiple nevoid basal cell carcinoma syndrome, neurofibromatosis, Fanconi anemia, Bloom syndrome, familial polyposis coli,

retinoblastoma, Gardner syndrome, polyendocrin adenomatosis, multiple exostosis, tylosis and esophageal cancer, thyroid carcinoma with amyloidosis, Werner syndrome ataxia-telangiectasia, and Chediak-Higashi syndrome. Cancers of the skin in which genetic factors may play a role in the etiology include: Kaposi sarcoma, generalized keratosis canthoma, and malignant melanoma. Heritable disorders of metabolism which predispose to skin cancer include: xeroderma pigmentosum, albinism, and phenylketonuria. At the subcellular level, the two most probable theories on the origin of cancer involve either somatic mutation or epigenetic mechanisms. The first theory holds that the fundamental event is a change in a gene or genes, probably due to a chemical reaction involving DNA. Epigenetic theories hold that the decisive step occurs extragenetically; such theories are based largely on the process of gene regulation in bacterial system and in higher forms. Gene regulation appears to be effected by small molecules which combine with repressors in microorganisms and alter the affinity of the repressor for DNA. In higher forms, regulator substances (hormones) combine with receptors; the resulting complex then alters the binding of nuclear proteins to segments of chromosomes. (112 refs.)

77-0079 Genetic Predisposition to Breast Cancer. (Eng.) Anderson, D. E. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumour Inst., Houston, TX 77025) *Rec Results Cancer Res* 57: 10-19; 1976.

When breast cancer patients with early and bilateral disease were considered, the risk to first-degree relatives was estimated to be 9.5. For relatives of patients with postmenopausal and unilateral breast cancer, the risk was 1.3-1.9. If the results for the two groups are pooled, the resulting risk ratio is about 2, which is the figure often cited for the genetic risk for breast cancer. There appears to be an inherited type of breast cancer, in which the daughters have a 30%-35% probability of developing breast cancer. Reduction of heterogeneity among breast cancer patients by dividing them into groups (age at onset, bilaterality) can permit a more realistic estimate of genetic risk. (38 refs.)

77-0080 Genetic and Familial Aspects of Liver Cirrhosis and Hepatocellular Carcinoma. (Eng.) Ohbayashi, A. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 43-51; 1976.

The familial and genetic aspects of hepatocellular carcinoma (HCC) and liver cirrhosis are discussed. The familial occurrence of cryptogenic cirrhosis in adults is rare in Europe and the US, but in Japan there have been reports of 10 families with clustering of chronic liver disease from 1963-1972. In these cases, the onset was usually insidious. Chronic hepatitis, cirrhosis, and HCC occurred frequently among adult members. A successive occurrence of the disease for two generations was recognized in 7/10 families, and the mother

and/or her siblings were inevitably affected in all 7. Infections with hepatitis B (HB) virus occurred often among family members, principally from mother to child, and many of the infected persons became carriers of HB antigen. Some of them developed chronic hepatitis, cirrhosis, and eventual HCC as adults. The development of viral hepatitis must depend on a complex interaction between HB virus and the immune response of the host, particularly cell-mediated immunity. There may be a genetic factor, ie, an inadequate immunological response to HB virus, which allows the virus to persist in the host. Further surveys on families of patients with chronic liver disease and HCC are needed for understanding of the interplay of immunity with neoplasia. HCC without cirrhosis is relatively rare in humans. A total of 89.2% of HCC in the US has been reported as complicated by cirrhosis. No familial clustering of HCC without cirrhosis or other preexisting hepatic changes has as yet been reported in Japan, and the relationship between HB antigen and HCC without cirrhosis or fibrosis is still largely unknown. (44 refs.)

77-0081 **Pathology of Coeliac Disease.** (Eng.) Thompson, H. (No affiliation given) *Curr Top Pathol* 63: 49-75; 1976.

The malignant complications of celiac disease are assessed. Malignant lymphoma has been demonstrated in 13/31 necropsy cases. The tumor occurs as a multicentric lesion with circumferential ulcerating lesions, nodular ulcerating lesions, and small ulcers or nodules in the mucosa. Many of the patients had celiac disease for > 20 yr, and some had been treated with a gluten-free diet. Other patients had a short history of adult celiac disease, but the disease may have been present for many years in an occult or latent form. The lesions may present as strictures, as a solitary lesion, or as occasional diffuse infiltration over short segments. Ulceration and perforation of intestinal lesions are serious hazards. Perforating lesions may be difficult to differentiate from simple ulceration, but the appearances of neoplastic reticulum cells infiltrating the muscularis propria at the edge of the perforation are characteristic. In the present series, the primary site was the small intestine in seven cases (jejunum 2, midileum 4, terminal ileum 1), stomach in one case, and lymph nodes in five. Multiple lesions were present in the gastrointestinal tract in 7 cases, and metastases were found in 10. Clinical diagnosis of malignant lymphoma during life has been established by lymph node biopsies, intestinal resection, partial gastrectomy, liver biopsy, diagnostic cytology of peritoneal and pleural fluid, peritoneal biopsy, and skin biopsy. Unexplained clinical deterioration, relapse on a gluten-free diet, or failure to respond to a gluten diet should stimulate a search for enlarged or palpable lymph nodes, and lymph node biopsy should be carried out as a preliminary step. (59 refs.)

77-0082 **Polyps and Cancer of the Large Bowel.** (Eng.) Enterline, H. T. (No affiliation given) *Curr Top Pathol* 63: 95-141; 1976.

Polyps and cancer of the large bowel are discussed. There is a diversity of types of lesions that may present as polyps of the colon or rectum. Colonic adenoma and its variants are significantly associated with carcinoma. Of the adenomatous polyps, the large polyps (mixed and villous forms) are at the highest risk of becoming malignant. Most carcinomas of the colon develop within the adenoma. A discussion of metaplastic polyps covers lipomas, leiomyomas, neurofibromas and ganglioneuromas, carcinoids, and adenoma of colon. Pseudoinvasion, villous adenoma, development of carcinoma in villous adenoma, the relationship of adenoma to adenocarcinoma, age of patients with adenoma and carcinoma, site of adenomas and carcinomas, and the incidence of adenoma and its coexistence with carcinoma are assessed in a discussion of the basic histogenesis of colonic adenocarcinoma. (114 refs.)

77-0083 **The Endocrine Cells of the Gastro-Intestinal Tract and the Neoplasms Which Arise from Them.** (Eng.) Dawson, I. M. (No affiliation given) *Curr Top Pathol* 63: 221-258; 1976.

Benign or malignant tumors and hyperplasias of every known type of endocrine cell have been described or postulated. It is practical to classify them in terms of clinical behavior, the nature of their secretion (as measured by serum radioimmunoassay or analysis of tumor material), their site of origin, their structural histological pattern and histochemical reactions, and the ultrastructure and immunochemistry of their granules. Some neoplasms, especially those that are malignant, may contain few or no storage granules. Neoplasms with a similar function frequently have differing histological patterns, but those with similar patterns either have differing functions or no recognizable function at all. Some appear to secrete more than one hormone, either simultaneously or sequentially. Classification into tumor patterns histologically is valuable in tumors that produce no overt clinical or laboratory evidence of functional hormone secretion. The relationship of structure, ultrastructure, and immunology to function is described for gastrinomas, insulinomas, glucagonomas, A cell hyperplasias, endocrine tumors associated with water diarrhea and hypokalemia, 5-hydroxytryptamine-secreting tumors, and multiple endocrine syndromes. Patients may present clinically with symptoms and signs suggesting the hypersecretion of more than one hormone, which can be verified on serum or tumor immunoassay. This may result from multiple endocrine adenomas or hyperplasias, single endocrine tumors secreting more than one hormone, and inappropriate hormone secretion by other tumors. All hyperplasias or neoplasms of endocrine cells should be studied as fully as possible. (159 refs.)

77-0084 **The Precarcinomatous Phase of Ulcerative Colitis.** (Eng.) Riddell, R. H. (No affiliation given) *Curr Top Pathol* 63: 179-219; 1976.

The precarcinomatous phase of ulcerative colitis is examined.

The high-risk clinical group consists of patients with extensive or total colitis and a long history, particularly if the onset of the disease occurred before the age of 25. The distribution of colitic cancers varies from that observed in noncolitic cancers in that the former are more commonly seen in the proximal colon. If the macroscopic appearance of a dysplastic area actually giving rise to a carcinoma is considered, a "flat" area is closely related to basal cell dysplasia, and "polypoid" and "villous" areas are closely related to adenomatous dysplasia. The potential for the flat dysplasia to produce carcinomas with extensive local spread is apparent. Conversely, the more polypoid lesions produce mostly carcinomas that have not invaded the muscularis propria. Misplaced epithelium, either localized or diffuse, is a well-recognized feature of longstanding ulcerative colitis. Characteristically, these epithelia form mucin pools in the submucosa, are lined by normal epithelium, and connect with the surface mucosa. The pathogenesis is uncertain, but they probably arise as a result of re-epithelialization of deep submucosal ulcerations. Occasionally, misplaced epithelium is misdiagnosed as carcinoma purely because of the presence of mucus cysts in the submucosa. Finally, the detection of dysplasia on rectal biopsy should lead to serious consideration of proctocolectomy. (38 refs.)

77-0085 Xeroderma Pigmentosum. (Eng.) Mascaro, J. M. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 573-595; 1976.

A review is presented of the epidemiology and incidence of xeroderma pigmentosum and its etiology and pathogenesis, clinical features, pathology, differential diagnosis, treatment, and prognosis. The disease is now regarded as a complex hereditary process that manifests itself solely through cutaneous symptomatology or as a cutaneoneuroendocrine-somatic expression; it is probably the result of a complex metabolic error, in which the fundamental defect is the lack of one or several enzymes. The cutaneous and ocular manifestations of xeroderma pigmentosum are generally due to hypersensitivity to actinic light and especially to the UV rays of the solar spectrum. However, there are patients with a completely normal response to light. The causes of death are usually neoplastic cachexia through multiple metastases of a squamous cell carcinoma or a malignant melanoma, hemorrhages, secondary meningitis due to a neoplastic invasion, and intercurrent diseases such as tuberculosis. The fibroblasts of xeroderma pigmentosum patients with UV damage do not undergo DNA repair replication, but the relationship between this defect and carcinogenesis is neither simple nor obvious. (145 refs.)

77-0086 The Borderline Between Cancer and Noncancer: Interrelationships Between Stroma and Epithelium. (Eng.) Pinkus, H. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders

Co.): vol. 1, pp. 386-404; 1976.

Cancers of the skin are discussed in terms of borderlines between nonmalignant and malignant conditions. The progression from an innocuous to a malignant lesion is most frequently and most easily observed in actinic keratoses and less frequently in Bowen's dermatosis and in lesions induced by arsenic. Just as the origin of an actinic keratosis or a Bowen lesion is a cellular event due to the cells' biologic inability to break the basement membrane, so apparently is the progression from carcinoma in situ to invasive carcinoma. The following nine representative biologic characteristics of a cell are used to illustrate the possible stepwise progression from a normal to a malignant condition: respiration, hormonal control, cohesion, normal enzyme make-up, growth control, contact inhibition, normal protein make-up, stroma dependence, and polarity. In the normal cell, all of these systems are properly functioning. Partial loss or deviation of some functions characterizes a benign tumor cell. Additional disturbances or losses give the cell the character of lower or higher grades of malignancy. Metastasis is the one decisive proof of malignancy in skin tumors and demonstrates the ability of single tumor cells (or perhaps small aggregates) to establish themselves in foreign surroundings, multiplying independently of local tissue factors and inducing the host tissue to supply a nourishing stroma. Basal cell epithelioma is the principal occupant of the border zone between cancer and noncancer. The one feature that separates true basalioma from all of its benign congeners is the reactive inflammatory infiltrate that seems to indicate that the body recognizes a malignant tumor as "nonself." The epithelial cells are basically deranged and are malignant cells which are restrained by their dependence on the stroma. (76 refs.)

77-0087 Fine Structure of Skin Neoplasms. (Eng.) Merkow, L. P.; Salazar, H. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 351-385; 1976.

The histology of various benign and malignant skin neoplasms is reviewed. Among the malignant neoplasms, the ultrastructural features of invasive squamous cell carcinoma of the skin are identical to those of the same type of tumor in other organs. The epithelial neoplastic cells, either isolated or forming small groups or nests, appear loosely immersed within a connective tissue stroma. The cells are polygonal, with irregular outlines separated from each other by wide intercellular spaces containing a complicated mesh of interdigitating cytoplasmic microvilli. At points of contact, adjacent tumor cells are attached by typical trilaminar desmosomes associated with dense bundles of cytoplasmic tonofilaments. The squamous neoplastic cells have large nuclei with irregular outlines, densely clumped chromatin, and large irregular nucleoli. The cytoplasm contains large numbers of organelles, including pools of glycogen and irregularly distributed bundles of tonofilaments. Melanoma cells may originate from epidermal melanocytes rather than from pig-

mented cells of the upper dermis. The neoplastic cells are usually arranged in large groups, closely packed and related to each other either by apposition of plasma membranes or by interdigitation of cytoplasmic pseudovilli that project within the narrow intercellular spaces. Melanoma cells are either rounded or angulated, with large pleomorphic nuclei. Large nucleoli and intranuclear inclusions are frequently seen. Malignant blue nevus, a rare melanotic neoplasm of the skin, closely resembles the more common cellular blue nevus. Pleomorphism of the tumor cell pattern from one area to another appears to be the hallmark of this neoplasm. The following benign neoplasms are also described: intradermal nevus (neuronevus), leiomyoma cutis, capillar hemangioma, fibrous xanthoma, neurofibromatosis, keratoacanthoma, and molluscum contagiosum. (14 refs.)

77-0088 **Lumbar Puncture and Epidermoid Tumours.** (Eng.) Anonymous (No affiliation given) *Lancet* 1(8012): 635; 1977.

Intraspinal epidermoid tumor, a rare complication of lumbar puncture (LP), has been reported in the literature in infants and young children. However, no tumors have yet been reported after LP with a modern disposable hollow needle. The child must be held firmly, with the spine straight and well-flexed. If the operator is careful to enter precisely in the midline, advancing the needle accurately in the sagittal plane, perpendicularly or slightly cephalad, this procedure should present no problem. A stylet should always be used and it should be examined carefully for fit, since even disposable LP needles occasionally have ill-fitting stylets. (7 refs.)

77-0089 **Skin Carcinogenesis.** (Eng.) Albert, R. E. In: *Cancer of the Skin. Biology-Diagnosis-Management.* Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 111-136; 1976.

An overview is presented of the current status of skin carcinogenesis research involving ionizing radiation, UV radiation, chemical carcinogens, and viruses. Subcellular, cellular, and tissue effects of radiation are discussed, and data are presented on the temporal aspects of tumor formation and radiation dose-response relationships. In the case of ionizing radiation, consideration is given to the effects of penetration depth, linear energy transfer, nonuniform surface application, and dose fractionation and to the relationship between follicle atrophy and tumor development. Despite impressive advances in our knowledge of the neoplastic process, it is not known how cells acquire a defective control of proliferation and how they develop metastatic properties. The mechanisms by which carcinogens produce these cellular disturbances and the reasons for wide differences in susceptibility are also unknown. Answers to these questions would greatly facilitate the identification and control of environmental carcinogens. (124 refs.)

77-0090 **Cheilitis.** (Eng.) Katzenellenbogen, I.; Sandbank, M. In: *Cancer of the Skin: Biology-Diagnosis-Management.* Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 607-634; 1976.

Different types of cheilitis and their relationship with lip cancer are reviewed. Cheilitis actinica belongs to the facultative precanceroses in the broader sense of the term. Persons with existing malignancies in the face and concomitant chronic actinic cheilitis are more prone to lip cancer. Malignant transformation of actinic cheilitis is clinically expressed by the appearance of horny prominences, ulcers, and deep fissures. Cancer of the lower lip may occur years after the cheilitis has been clinically cured. The histologic criteria for the malignant changes of actinic cheilitis are manifested by atypia and loss of polarity of the basal layer cells, hyperchromatism of the nuclei, increased numbers of mitotic figures, and individual cell keratinization. Histologic examination of the entire mucosa of the lip of circumscribed carcinoma has disclosed considerable deterioration of the area with a normal clinical appearance. This deterioration could explain certain relapses and new malignancies in the mucosa of the lip following radical operation for the cancer and many so-called "de novo" cases of lip cancer. Cheilitis abrasiva precancerosa of Mangano is a late variant of cheilitis actinica and is precancerous in the strict sense. Sun exposure is implicated as the cause of lip cancer because of the prevalence of the cancer in the sun-damaged lower lips of outdoor workers and in light-complexioned persons who have less inherent protection. (115 refs.)

77-0091 **Epidermodysplasia Verruciformis.** (Eng.) Baptista, A. P.; Araujo, A. B. In: *Cancer of the Skin: Biology-Diagnosis-Management.* Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 596-606; 1976.

Epidermodysplasia verruciformis (EV), a virus infection of the verruca vulgaris type, is discussed in terms of the malignant transformation associated with this precancerous dermatosis. One of the most important characteristics of EV is the frequency with which one or more lesions undergo cancerous transformation (22%). Carcinomas usually develop between 20 and 30 yr of age and predominate in regions exposed to light, especially the face. In the majority of cases, the carcinomas are squamous cell; however, basal cell carcinomas and, less frequently, Bowen's disease are also found. In cases of multiple malignancies, any combination of these cancers can be found. The relationship between the verrucous lesions of EV and these carcinomas has been confirmed by observations of the cancerous cells, in which there are the same cavity formations as in the verrucous lesions, and observations of the areas of gradual transition between carcinomas and verrucous lesions. The frequency of malignant transformation and the young age at which it generally develops justify the consideration of EV as a precancerous dermatosis. Even though the behavior of the virus in malignant degenera-

tion of EV is similar to that in Shope's papilloma (the virus ceases to be detectable in the tumor cells), it has not been possible to demonstrate satisfactorily the cancerous potential of the virus in EV. One possible mechanism of malignant transformation that has been postulated involves the virus giving rise to a lesion that is essentially lithic. Viral multiplication then occurs in the epidermal cells of a normal individual, whereas a simultaneous lysis and transformation of the epidermal cells occurs in certain genetically abnormal individuals. (49 refs.)

- 77-0092 **Cutaneous Horns.** (Eng.) Bart, R. S. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 557-572; 1976.

The malignant potential and pathology of various histologic cutaneous horns are discussed. Cutaneous horns associated with actinic keratosis, with or without early squamous cell carcinoma, are common and may be either premalignant or malignant. Horns associated with frank squamous cell carcinoma are rare but malignant. The incidence of cutaneous horns associated with Bowen's disease is rare; such horns are associated with carcinoma in situ. Horns found upon basal cell epithelioma are rare and malignant. So-called "penile horns" are uncommon and may range from benign to malignant. The causes of cutaneous horns are those of the various entities found at their bases. The pathogenesis is poorly understood for most of these lesions. Regarding actinic keratoses and squamous cell carcinomas, which are better understood from the standpoint of pathogenesis, cutaneous horns rising upon these entities occur much more frequently in light-eyed individuals, ie, those who by virtue of associated fair skin are more likely to incur actinic damage. It is much more common to find associated premalignant and malignant skin lesions (actinic keratoses, basal cell epitheliomas, and squamous cell carcinomas) other than the cutaneous horns themselves, when the horns are upon actinic keratoses and squamous cell carcinomas than when they are upon benign bases. (32 refs.)

- 77-0093 **Leukoplakia.** (Eng.) Hornstein, O. P. In: *Cancer of the Skin: Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 524-556; 1976.

Leukoplakic and leukokeratotic lesions of the oral cavity are reviewed. Definite precancerous leukoplakias include: "speckled" leukoplakia, Bowen's disease of the mucosa, "oral florid papillomatosis," and some varieties of hereditary polykeratoses. Although many of the leukoplakic conditions remain in a benign stage throughout life or disappear after removal of the causative factors, some may change facultatively into premalignant lesions if the conditioning irritations continue for a long time (inflammation in syphilitic glossitis or in the pemphigoid variety of lichen ruber). If irregular thickening and infiltration of the leukoplakia is present, a

precancerous lesion should be suspected. The "speckled" type of leukoplakia changes into malignancy in a high percentage of cases. Marked induration or localized ulceration within a leukoplakic area is pathognomonic of cancer formation. Since the risk of inducing metastatic spread to lymph nodes may be increased at this stage by minor biopsies, wide excision of the entire lesion should be carried out on first admission. One of the more important factors involved in the etiology of intraoral and labial leukoplakias is local contact with tobacco. Snuff, applied habitually in the lower sulcus of the buccal mucosa, may give rise to leukoplakia or even carcinoma. Regarding the etiology of lip cancer, exposure to sun, wind, and frost is associated with a higher incidence of this type of cancer. Habitual pipe smoking or tobacco chewing is probably another but probably less important etiologic factor. In terms of prognosis, the absolute 5-yr survivals for malignant tumors of the lip, tongue, floor of the mouth, buccal mucosa, gingiva, and palate are 67.7%, 26.9%, 33.7%, 37.0%, 33.9%, and 26.7%, respectively. The corresponding stage I or II 5-yr survivals are 85.2%, 53.0%, 59.5%, 60.6%, 62.7%, and 46.6%, respectively. (161 refs.)

- 77-0094 **Biochemical Abnormalities in Chronic Erythremic Myelosis.** (Eng.) Kass, L. (Dept. Internal Medicine, Simpson Memorial Inst., Univ. Michigan, Ann Arbor, MI 48109) *Br J Haematol* 35(2): 169-175; 1977.

In this review of chronic erythremic myelosis (CEM) biochemical abnormalities discussed include those of DNA and histone synthesis, of glycogen metabolism in erythroblasts, and of iron storage as ferritin. The activity of vitamin B₁₂ methyltransferase is 3-4 × higher in sonicates of marrows from CEM patients than in normal marrow sonicates; this may be a reflection of the neoplastic potential of erythroid cells in CEM. Elevated levels of this enzyme may explain the ineffectiveness of vitamin B₁₂ in CEM. (64 refs.)

- 77-0095 **Immune Phenomena in Lymphogranulomatosis: A Key to Etiology and Pathogenesis?** (Ger.) Gallmeier, W. M. (No affiliation given) *Haematol Bluttransfus* 18: 81-87; 1976.

Immunological phenomena in Hodgkin's disease (HD) are reviewed. The peripheral blood lymphocyte count is usually normal during the early stages, but it decreases with disease progression. Humoral immunity appears to be normal during the early stages, but cellular immunity is altered. The B-lymphocyte counts in the blood of most patients are normal or slightly elevated; T-lymphocyte counts may be reduced in some cases and possibly increased in the spleen. Increased Epstein-Barr virus antibody titers were found in the sera of patients with unfavorable prognosis. There is no known tumor or virus antigen for HD. According to a current theory, human lymphocytes are selectively infected by oncogenic viruses, the infected cell generates an immune reaction as

early as the preneoplastic phase, and the T-cell-mediated immune reaction intensifies after malignant transformation and the formation of Hodgkin's and Reed-Sternberg cells. The immunological disturbances observed in HD are mainly due to the increased activity of the T-lymphocyte system in defense reactions against the tumor rather than to the malignant transformation of these lymphocytes. The immune reactions involved in HD include not only those of normal T lymphocytes against abnormal cells, but also reactions of malignant Hodgkin's cells against normal lymphocytes, at least during one phase of the disease. The reactions are assumed to lead to a complete lymphocyte depletion in the lymphatic organs and to the selection of fully autonomous, highly malignant cells that are the source of hematogenous metastases. (no refs.)

77-0096 Proliferation and Growth of Lymphatic Cell Populations in Malignant Lymphoma. (Ger.)

Trepel, F. (SFB 112 - Zellsystemphysiologie, Universität Ulm, Ulm, W. Germany)) *Haematol Bluttransfus* 18: 33-47; 1976.

Studies on the proliferation and growth of lymphatic cells in malignant lymphomas are reviewed. Malignant lymphoma is due to the prevalence of neoformation over the elimination of lymphatic cells. Interim stationary phases represent a temporary equilibrium between the two processes. Since the generation time of most proliferating malignant lymphomas is similar, differences in cell production among different lymphomas are due to differences in the growth fraction. Since proliferation takes place only in the larger cells, they determine the growth fraction. Thus, large-cell lymphomas show the most intense cell production and the highest degree of malignancy. The lymphoma growth rate is substantially lower than would be expected from the growth fraction, a result of the immediate death of most new cells in large-cell lymphomas and of the transition of most new cells to the G_0 phase in small-cell lymphomas. Non-Hodgkin's lymphomas grow exponentially and are of a monoclonal origin, but Hodgkin's lymphomas are of a polyclonal origin. The growth rate of the normal lymphatic cell system in early childhood is only slightly lower than that of chronic lymphocytic leukemia and plasmacytoma cells. The essential difference between normal cells and malignant lymphoma cells lies in cell elimination; in normal cells, neoformation and elimination are subject to the same regulatory mechanisms, but in lymphoma cells, they are not regulated. The cell-elimination rate in large-cell lymphomas appears to be determined by unspecific factors, eg, trophic conditions. (53 refs.)

77-0097 The Epidemiology and Genetics of the Chronic Leukaemias. (Eng.) Gunz, F. W. (No affiliation given) *Clin Hematol* 6(1): 3-20; 1977.

The epidemiology of chronic granulocytic leukemia (CGL) and chronic lymphocytic leukemia (CLL) is reviewed. The

incidence of leukemia is higher in men, with the sex ratio varying from 1.05 to 2.25. The age distribution of leukemia shows a curve with a narrow peak between the ages three and five and a broader and higher peak at ages over 50. The majority of the childhood cases are acute leukemias. CGL occurs rarely but constantly in childhood and then increases in proportion, yielding a broad peak in middle age. CLL is very rare before the age of 40 and increases steadily thereafter. In typical Western populations CGL comprises about 15% of all leukemias, and CLL, about 25%. A number of factors may contribute to the causation of leukemia and include ionizing radiations, chemical agents, and a variety of microorganisms. Ionizing radiation is the only factor that is recognized as leukemogenic in man. Genetic studies indicate that the predisposition to contract leukemia is polygenic in origin; that is, in families with CLL members there is a relatively strong predisposition or a low threshold towards the disease. In CGL there is no substantiating evidence, and it is assumed that this type of leukemia usually arises from the interaction of nongenetic factors. (39 refs.)

77-0098 Cytogenetics in Human Leukemia. (Eng.) Trujillo, J. M. (Dept. Lab. Medicine, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX) *Pathobiol Ann* 6: 203-220; 1976.

The contributions of cytogenetics to the study of human leukemia are reviewed. The presence of the Philadelphia chromosome (Ph^1) in cells from the hematopoietic tissue of patients with chronic granulocytic leukemia (CGL) seems to have definitive clinical implications, as indicated by the fact that the Ph^1 -negative CGL patient has a poorer prognosis than the Ph^1 -positive one. Its presence in the myeloid, erythroid, and megakaryocytic cells provides strong evidence in favor of the existence of a common hematopoietic precursor cell (stem cell) distinct from the lymphocytic cell, which appears to be involved. The widespread presence of Ph^1 indicates that CGL is a condition that affects the entire hematopoietic system. Although blastic crisis in CGL is not always accompanied by additional karyotypic aberrations, the late appearance of new, chromosomally abnormal cells in Ph^1 -positive and -negative patients invariably signals the acute or terminal phase of the disease. Chromosome-banding studies in several Ph^1 -positive CGL patients in the acute phase revealed that the additional chromosomal alterations are nonrandom. The reported incidence of aneuploidy in acute leukemia varies from 29%-100%. Sequential chromosomal studies have demonstrated that in the aneuploid leukemias a favorable response to therapy is marked by two events: (1) an early disappearance of the aneuploid and/or pseudodiploid clones; and (2) a reappearance and/or increase in the number of diploid cells. Thus, whenever present, the chromosomal alterations specifically define the leukemia cells. Cytogenetic investigations in experimental tumors tend to support the thesis that karyotypic changes may be agent-specific, but this requires more investigation in the human hematologic disorders. The demonstration by cytogenetic

studies of the nonrandom pattern of chromosomal changes in human leukemia constitutes a considerable advance toward a better understanding of this disease. (87 refs.)

- 77-0099 **The Cytogenetics of Chronic Granulocytic Leukaemia.** (Eng.) Lawler, S. D. (No affiliation given) *Clin Hematol* 6(1): 55-75; 1977.

The history of the Philadelphia (Ph¹) chromosome and the cytogenetics of chronic granulocytic leukemia (CGL) are reviewed. The Ph¹ chromosome involves a deletion of chromosome number 22; the deleted material is translocated to another autosome, usually a number 9, t(9;22)(q34;q11). This translocation in the chronic phase accounts for about two-thirds of the cases when no additional abnormalities are present. Clinical differences between patients showing usual and unusual translocations of the 22q cannot be detected. Some phenotypically normal males with XY lymphocytes may have t(Ph¹) myeloid cells that lack a Y chromosome. In males with CGL this may represent some form of premature aging of the bone marrow. Another abnormality, which may be present in CGL, is trisomy of chromosome number 8. Metaphases with two Ph¹ chromosomes without duplication of the 9q+ chromosome are observed in about 10% of cases in the chronic phase. Additional translocations occur in about 8% of chronic phase cases. Patients diagnosed as having CGL but lacking the Ph¹ chromosome usually present atypical clinical features. Ph¹ negative patients have a higher median age and are usually men. Median survival for Ph¹ positive patients is 40 mo; whereas, the median survival for Ph¹ negative patients is only 8 mo. Because of this difference in prognosis the presence or absence of the Ph¹ chromosome should be determined in patients with CGL. (60 refs.)

- 77-0100 **Cell Kinetics in Chronic Granulocytic Leukemia (CGL).** (Eng.) Stryckmans, P. A. (Euratom, Univ. Brussels, Belgium) Debusscher, L.; Collard, E. *Clin Hematol* 6(1): 21-40; 1977.

The cell kinetic characteristics and functional activities of granulocytes in chronic granulocytic leukemia are reviewed. Three different phases of CGL are important in the study of the pathogenesis of the disease. The phase at diagnosis and during relapse is characterized by a high leukocyte count and by a heavy infiltration of the spleen and marrow by leukemia cells. The phase of unmaintained remission is characterized by an almost normal blood picture with persistence of the Philadelphia (Ph¹) anomaly. The phase of blastic transformation or metamorphosis is usually irreversible and fatal. In active CGL with increased leukocyte count, the effective production of granulocytes is always increased. Cross transfusions of normal granulocytes to CGL patients and vice versa show that the increased blood-transit time of the polymorphonuclear leukocytes (PMN) is due mainly to cellular, rather than extracellular, factors. During remission of CGL the total blood granulocyte pool (TBGP), the granulocyte turn-

over rate (GTR), and the half life of the granulocytes return to normal. Since a PMN is the final product of a myelocyte division, an increase in the turnover rate of PMN must be accompanied by an increase in myelocyte production. The kinetic characteristics of myeloblasts in CGL appear as a secondary phenomenon associated with an increase in the total granulocytic cell mass, suggesting that the myeloblasts are still sensitive to the action of some regulatory mechanism. In blastic transformation, myeloblasts are abundant in the blood and the marrow but show signs of concomitant maturation defects and slower proliferation. The maturation defect is shown by the absence or decrease of PMN in blood and marrow films. (100 refs.)

- 77-0101 **In Vitro Culture Studies in Chronic Granulocytic Leukaemia.** (Eng.) Moore, M. A. (No affiliation given) *Clin Haematol* 6(1): 97-112; 1977.

Studies investigating the existence and nature of humoral regulators are reviewed. Colony forming cells (CFU-c) are morphologically undifferentiated transitional mononuclear cells committed to granulocyte-monocyte differentiation and comprise 0.1- to 1% of the total nucleated cell population of the marrow. In untreated chronic granulocytic leukemia (CGL), increased numbers of CFU-c are present, and the colony-forming capacity of the marrow is normal to increased. Cytogenetic studies of colonies derived from CGL patients have generally shown the presence of Ph¹ metaphases. In CGL normal maturation of CFU-c takes place yielding colonies composed of mature neutrophils, eosinophils, monocytes, and macrophages. The proliferation of CGL bone marrow in liquid culture is two- to three-fold greater than normal, indicating an increased incidence of committed stem cells. Cellular maturation is normal in these cultures with granulocytes and actively replicating macrophages functioning normally. The development of blast transformation may occur in a sequence of progressively more abnormal stem cell clones evolving sequentially from the original Ph¹ clone. Multiple clonal progressions have been observed in some patients and in vitro. Analysis of the in vitro growth characteristics of marrow or blood from patients diagnosed as having blastic transformation showed defects in proliferation and maturation that distinguished this phase from the chronic phase of the disease. (50 refs.)

- 77-0102 **Cell Kinetics in Chronic Lymphocytic Leukemia (CLL).** (Eng.) Stryckmans, P. A. (Debusscher, L.) Collard, E. *Clin Hematol* 6(1): 159-167; 1977.

A review of studies with ³H-thymidine and autoradiography have shown that DNA synthesis is higher in the lymph nodes in normal individuals and in two chronic lymphocytic leukemia (CLL) patients than in the blood. Comparison of the normal and CLL data in these studies shows that the overall CLL ³H-thymidine labelling index (LI) was 0.65 and 1.41% and that the normal LI was 0.5% ± 0.2. Using double labeling

methods, the duration of DNA synthesis in lymphocytes was 11.8 hr in the lymph nodes and 11.6 hr in the spleen. The 1-hr ^3H -thymidine LI for peripheral blood was 0.1 ± 0.1 in normal individuals; it ranged from 0 to 0.66% in vitro and from 0 to 0.15% in vivo in CLL patients. Continuous infusion studies indicate that the blood lymphocyte fractional turnover rate is lower in CLL but that the absolute turnover rate is higher in CLL patients than in normal individuals. CLL and normal lymphocytes both undergo rapid exchange with the extravascular pool of lymphocytes, but recirculation of the lymphocytes does not proceed normally in CLL. This abnormality may be related to either the B nature of the CLL lymphocyte, the leukemic nature of the CLL lymphocyte, or mechanical factors, such as crowding of the extravascular pool. (42 refs.)

77-0103 Hairy Cell Leukemia. (Ger.) Löffler, H. (Zentrum für Innere Medizin, Justus Liebig-Universität, Giessen, W. Germany) Roux, A.; Fischer, J.; Desaga, J. F.; Pralle, H.; Graubner, M. *Haematol Bluttransfus* 18: 255-272; 1976.

The nosological, morphological, cytochemical, and therapeutic aspects of hairy cell leukemia are described. Electron microscopic investigations have shown that hairy cells have oval nuclei, a condensed marginal chromatin, and often small nucleoli. The cytoplasm has numerous villi, vesicles, and large oval mitochondria. Certain properties of hairy cells suggest a similarity to monocytes, but hairy cells lack three important characteristics of monocytes: myeloperoxidase, lysozyme, and pronounced levels of α -naphthylacetate esterase and naphthol-AS-D acetate esterase. Most arguments suggest that hairy cells are B-lymphocytic. Hairy cells may originate from a cell that occurs normally in the body, but is not released into the bloodstream in normal subjects. Mitoses are rare. (1 refs.)

77-0104 Differential Functions of Glial and Schwann Cell Tumor Clones. (Eng.) Wechsler, W. (Max-Planck-Institut für Hirnforschung, Abteilung für Allgemeine Neurologie, Ostmerheimer Strasse 200, D5000 Cologne 91, W. Germany) *Arzneim Forsch* 27(2): 457-458; 1977.

Inbred rat and mouse strains were treated systematically during the perinatal stages of development with ethylnitrosourea to produce tumors of the central and peripheral nervous system. These clones, which are reviewed briefly, include rat glioma clones C6 and CDF, and Schwann cell neurinoma clones RN-2 and IRN-6 (a mycoplasma-free subclone of cell line RN-2). It still must be determined to what extent the cell surface antigens found on rat Schwann cell tumors are related to normal, embryonal, or pathological (eg, tumor-specific) antigens. (14 refs.)

77-0105 Surgical Aspects of Granulosa Cell Tumors. (Ger.) Ziegler, A. (Chirurgische Klinik, Stadthospital Waid, CH-8037 Zurich, Switzerland) *Helv Chir Acta*

43(5/6): 645-647; 1976.

Studies on the clinical and epidemiological aspects of granulosa cell tumors of the ovary are reviewed. These tumors, which account for 1% of all ovarian tumors, are hormonally active, unspecific, malignant epithelial tumors. They can be unilateral or bilateral. Their malignancy decreases with increasing degree of differentiation. They usually occur at an advanced age, but they have been observed in children. (4 refs.)

77-0106 Ovarian Teratomas and Genetics of Germ-Cell Formation (Letter to Editor). (Eng.) Riley, P. A. (Div. Pathology, Univ. Coll. Hosp. Medical Sch., London WC1E 6JJ, England) *Lancet* 1(8007): 362-363; 1977.

Some researchers argue that benign ovarian teratomas do not arise from a random error in meiosis, but rather from an inherited gene that influences the fate of the second polar body and may promote fusion with the ovum to initiate a parthenogenic tumor. Although this notion may prove to be correct, it is contended that, on the basis of the chromosome analyses of these researchers, fusion is indistinguishable from failure of the second meiotic division. The evidence relating to an inherited component emphasizes that the genetics are unlikely to be simple. Nevertheless, the extreme rarity of multiple ovarian teratomas (compared to the number of maturing oocytes) and the variable expression of the predisposition to develop these tumors suggest that a degree of randomness exists in teratogenesis. This is consistent with the acquisition of a final mutation during meiotic prophase in a manner proposed (by the authors) in a simplified scheme for a single locus. The initial normality of such a gene would be preserved by the malignant behavior of the obligatory homozygote, which would result at the first meiotic division of any oocyte with an inherited mutation at this locus. Therefore, it is not conceded that there is any inconsistency between the evidence advanced by the previous researchers and the present hypothesis. (7 refs.)

77-0107 Selection, Screening, and Isolation of Temperature-Sensitive Mutants of Avian Sarcoma Viruses. (Eng.) Wyke, J. A. (Dept. Tumour Virology, Imperial Cancer Res. Fund, London, England) *Methods Cell Biol* XIV: 251-264; 1976.

Methods for increasing the efficiency for screening, selection, and isolation of temperature-sensitive mutants of avian sarcoma viruses are described, evaluated and suggested. (37 refs.)

77-0108 A Critical Review of Histochemical and Electronmicroscopical Studies of Total Prostatectomy Specimens. (Eng.) Kirchheim, D. In: *Prostatic Disease. Proceedings of the American-European Symposium held in Vienna, November 3-5, 1975.* Physicians Association for Con-

tinuing Education. (Vienna, Austria): pp. 357-361; 1976.

Sections of 30 total prostatectomy specimens were submitted to a battery of histochemical enzyme reactions. Surgery was performed because of a clinical diagnosis of Stage B or II carcinoma. Histologically, 6 of the 30 specimens were actually Stage C or III lesions. The findings of invasive growth in many Stage B lesions indicated the malignant potential of these lesions. Histochemically, the cells showed positive reaction to various oxidative and hydrolytic enzymes with the exception of aminopeptidase, which was absent in the majority of the cancer cells. Acid phosphatase was usually decreased in prostatic cancers. In anaplastic prostatic cancer cells, differentiation became so deleted that the acid phosphatase stain was not visible. Electron microscopy of these cells showed the remnants of the typical organelles. Localized B lesions contained predominately differentiated adenocarcinoma. The gradual decrease in acid phosphatase was parallel with the morphologic dedifferentiation. (1 refs.)

- 77-0109 The Surgical Management of Pulmonary Metastases.** (Eng.) Homes, E. C. (Div. Oncology, Dept. Surgery, UCLA Medical Sch., Los Angeles, CA) Ramming, K. P.; Eilber, F. R.; Morton, D. L. *Semin Oncol* 4(1): 65-69; 1977.

The criteria for evaluating and treating patients with pulmonary metastatic disease are discussed based on treatment of 120 patients who underwent pulmonary resection for metastatic lesions. Criteria used in evaluating candidates for pulmonary resection are controlled primary disease, no evidence of metastasis to other viscera, and a tumor doubling time (TDT) greater than 40 days. TDT can be determined by successive chest roentgenograms-- at 2 wk and again at 1 mo. The histology of the primary lesions is an important consideration because certain sarcomas metastasize to the lung before involving other viscera. Patients with pulmonary metastases who have TDT greater than 40 days generally respond well to pulmonary resection alone. Patients with a TDT of less than 40 days, or who have other metastatic diseases, are considered highly experimental. Chemotherapeutic regimes involving high dose methotrexate with citrovorum rescue and adriamycin are given adjunctively to pulmonary resection. The authors reported that 8 of 10 sarcoma patients treated by this regimen were free of disease at a mean follow-up interval of 10 mo. (18 refs.)

- 77-0110 Pathways of Metastatic Spread of Malignant Tumors.** (Eng.) del Regato, J. A. (Dept. Radiology, 13000 N. 30th St., Tampa, FL 33612) *Semin Oncol* 4(1): 33-37; 1977.

Several pathways of metastatic spread of tumor cells are described, and the factors involved are reviewed. In the transport of tumor cells, it is emphasized that the viability of detached neoplastic cells appears to be more easily preserved when they move slowly in the lymphatic channels and the

body fluids of closed systems or cavities. The routes discussed include lymphatic, thoracic duct, venous, vertebral vein system, serous cavity, and cerebrospinal spreads. The lung is discussed as a secondary source of metastatic spread. Unusual forms of spread and metastatic paradoxes are also commented upon. (38 refs.)

- 77-0111 A Pathobiologic Overview of Metastasis.** (Eng.) Weiss, L. (Cancer Res., Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263) *Semin Oncol* 4(1): 5-17; 1977.

Any tendency for cancer cells to separate from solid tumors is not an inherent, cancer-specific property of these cells but rather the effects of growth and/or degeneration, which themselves are at least partially dependent on interactions between normal and cancerous cells or tissues. The hypotheses that thrombogenesis is in some way associated with the arrest of circulating cancer cells and that if arrest could be prevented, the circulating cells would be destroyed by mechanical and humoral factors have led to attempts to prevent metastases by anticoagulant therapy. Immune factors play a role in the growth and dissemination of cancer in laboratory animals. The significance of this role in man has yet to be established. Immunologic tests for cancer and/or its prognosis remain to be evaluated. Only a small proportion of the total cells is expected to be released from the primary tumor, and of these, only a small proportion is expected to survive the trauma of dissemination and arrest. (36 refs.)

- 77-0112 Mechanisms and Prevention of Cancer Dissemination: An Overview.** (Eng.) Sugarbaker, E. V. (Miami, FL 33152; Ketcham, A. S. *Semin Oncol* 4(1): 19-31; 1977.

A model for tumor cell dissemination and the clinical aspects of the model that provide the rationale for treatment of dissemination are discussed. The model includes local invasion, its kinetic and metabolic aspects, and the stages of invasion, such as tumor cell entrance into and circulation in the bloodstream or the lymphatic system and arrest and proliferation of tumor cells in a distant organ or regional lymph node. Tumor cells can be arrested through the mechanisms of entrapment, fibrin, platelets, and anticoagulation. One important aspect of tumor metastasis is host tumor immunity. Surgeons should continue to use en bloc tumor resection plus other measures to minimize iatrogenic tumor dissemination. (107 refs.)

- 77-0113 Are 90% of Cancers Preventable?** (Eng.) Anonymous (No affiliation given) *Lancet* 1(8013): 685-687; 1977.

The possibility of reducing cancer incidence by 90% by the removal of specific environmental carcinogens is considered.

Removal of known carcinogens should lead to a substantial fall in cancer incidence, but with current knowledge the estimate of 90% seems optimistic. In British men the figure is probably closer to 50%-60%. Smoking is responsible for most lung cancers and for a smaller proportion of the cancers of the larynx, pharynx, esophagus, bladder, and pancreas, which together account for almost half the cancers that occur among British men. The elimination of smoking alone could, therefore, almost halve cancer incidence. The proportion of all cancers associated with other known carcinogens is rather small and includes the alcohol-related cancers, such as those of the esophagus and liver, occupational cancers, and iatrogenic cancers. The elimination of all these would probably not reduce the total cancer incidence by > 10%. The proportion of cancers that are environmentally determined is greater for men than for women, perhaps because a woman's exposure to the environment is more uniform. These observations suggest that the potential reduction in cancer incidence in women, while still considerable, is not of the same order of magnitude as that predicted in men. If cancer is to be prevented, changes in behavior, diet, alcohol consumption, and smoking will be necessary. (17 refs.)

77-0114 Patterns of Cellular Proliferation in Normal and Tumor Cell Populations. (Eng.) Garther, S. M. (Dept. Medicine, Univ. Washington, Seattle, WA 98195) *Am J Pathol* 86(3): 685-691; 1977.

Three types of cell mosaics have been used in mammalian studies: hemopoietic chimeras, mosaics formed by aggregation of preimplantation embryos, and mosaics resulting from X-chromosome inactivation. The problems investigated with these cell mosaics have included normal tissue organization, cell selection, primordial cell pool sizes, and tumor cell kinetics. The emphasis in this review is on the application of X-chromosome inactivation mosaics to the analysis of tumor cell proliferation. The first application of mosaicism to tumor ontogeny involved leiomyomas and demonstrated single-cell and independent origin of the tumors. Other tumor studies are reviewed, including those of presumed multiple-cell origin, especially those of hereditary origin (trichoepithelioma, neurofibroma) and viral etiology (malignant lymphoma in marmosets). In animals with hereditary tumors, every cell is susceptible, giving the initiating event a large target. The recent reports on the clonal nature of atherosclerotic plaques are also discussed. Most tumors with mosaic markers exhibit single phenotypes; these may indicate true single-cell origin or tumor progression from multicell origin. (28 refs.)

77-0115 The Relationship Between In Vitro Transformation and Tumor Formation In Vivo. (Eng.) Ponten, J. (Dept. Cell Biology, Wallenberg Lab., Univ. Uppsala, Uppsala, Sweden) *Biochim Biophys Acta* 458(4): 397-422; 1976.

In this review, the extent to which transformation in vitro

is equivalent to tumor induction in vivo was examined. The principal aspects of in vivo carcinogenesis, the explantation of tumor cells in vitro, the different types of in vitro cell transformation, and the value of implantation tests are discussed. DNA viruses and chemical and physical carcinogens may act according to the same general scheme in vivo and in vitro, but not enough in vitro studies have been made to warrant generalizations. There is the possibility of overestimating the carcinogenicity of chemical and physical agents for humans if testing is confined to inbred rodents. Transformation in vitro cannot be assessed indiscriminately by any known single parameter, such as lack of contact inhibition, criss-cross growth pattern, infinite life span, high terminal density, or loss of serum dependence. Each type of assumed transformation must be put into its proper biological setting, and the criteria for transformation must be meticulously compared with the behavior of histogenetically analogous normal cells and with tumor explants from the same cell types. (143 refs.)

77-0116 Adhesion of Malignant Cells to Capillary Endothelium (Letter to Editor). (Eng.) Ecanow, B. (Univ. Illinois, Medical Center, Chicago, IL) Gold, B. H.; Sadove, M. *JAMA* 237(12): 1201; 1977.

The known adhesive properties of fibrin and its continuous presence in the blood make it a logical agent to bind malignant cells to capillary endothelium. However, it is emphasized that the adhesiveness of fibrin is a function of its surface-active properties. A number of endogenous surface-active molecules (lecithin), as well as macromolecules (mucopolysaccharides and albumin), are also capable of absorbing onto cell surfaces and forming films that adhere readily to adjacent surfaces. (3 refs.)

77-0117 Control of DNA Helix Openings During In Vivo Normal and Neoplastic Cell Maturation. (Eng.) Frenster, J. H.; Landrum, S. R.; Masek, M. A.; Nakatsu, S. L.; Wilson, L. S. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 107-114; 1976.

Living and fixed human bone marrow spicules and lymph nodes of normal subjects and untreated patients with leukemia or lymphoma were examined by electron microscopy to the number and size of DNA helix openings with individual cells. A total of 123 normal differentiating granulocyte precursor cells, 189 normal differentiating RBC precursor cells, 97 normal mononuclear cells, and 22 normal differentiating megakaryocyte precursor cells were analyzed in living normal bone marrow spicules. A significant decrease in both size and number of helix openings was observed through the course of normal RBC, granulocyte, and megakaryocyte

maturation. A decrease was observed during *in vivo* nuclear blebbing maturation of neoplastic Reed-Sternberg cells in the lymph nodes of untreated patients with Hodgkin's disease. Openings increased during *in vivo* immune lymphocyte reactions. (36 refs.)

- 77-0118 **Worldwide Epidemiology of Premalignant and Malignant Cutaneous Lesions.** (Eng.) Gordon, D.; Silverstone, H. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 405-434; 1976.

The epidemiology of skin malignancies that have a causal relationship with sunlight is reviewed. The incidence of non-melanoma skin cancer increases as the geographic latitude decreases; it increases with age and is also higher in lightly pigmented ethnic groups. The incidence of melanoma follows the same pattern, but the correlation is more diffuse. Skin cancer mortality is discussed. Evidence is presented to support the theory that UV radiation in sunlight is a cause of skin cancer. Chemical carcinogens, ionizing radiation, and other factors can also cause skin cancer. The role of the epidemiologist in elucidating the problems of human carcinogenesis is discussed. (126 refs.)

- 77-0119 **Case Clustering in Cancer.** (Eng.) Caldwell, G. G. (Leukemia Branch, Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Atlanta, GA 30333) *South Med J* 69(12): 1598-1602; 1976.

Case clustering in cancer is reviewed. The results of statistical analyses of time-space clustering have not been entirely consistent in relation to leukemia. Although some studies produce positive results, none have uncovered any strong tendency for cases to cluster. Likewise, no particular time-space parameters have been found that consistently demonstrated clustering. It is uncertain whether low-level clustering may exist, particularly for childhood leukemia. Since the discovery of Burkitt's tumor, its irregular distribution in Africa, and the identification of Epstein-Barr virus in Burkitt's tumor cell cultures, particular attention has been given to this tumor as a potential model for viral oncogenesis. One important epidemiologic aspect has concerned questions of time-space case clustering for which, unlike for leukemia, evidence strongly suggesting a tendency for cases to cluster has been published. At least one individual cluster is described in detail in the literature: seven cases in Bwamba County, Uganda, over a 27-mo period. Several studies have concerned time-space clustering of cases of other lymphomas. Descriptions of individual clusters have been published, in some of which interpersonal contact has been a feature. In one instance, two cases of Hodgkin's disease occurred in dormitory roommates, and in another, four cases of lymphoma (most Hodgkin's disease) occurred in teen-aged girls in a small town in Idaho. Although no statistical analyses of time-space clustering of

cases of multiple myeloma have yet been made, one account of an individual instance of such clustering has been published. This concerned six cases in a northern Minnesota town, an incidence approx 20x greater than expected. The question of interpersonal contact clustering, aside from time-space considerations, has been raised primarily in relation to Hodgkin's disease. There is little evidence that time-space clustering is significant in the epidemiology of leukemia, lymphoma, Burkitt's tumor, and myeloma. However, clustering by interpersonal contact, particularly in Hodgkin's disease, does seem to occur. (40 refs.)

- 77-0120 **Subsequent Malignancy in Environmental Scrotal Cancers.** (Eng.) Waterhouse, J. A. (Queen Elizabeth Medical Centre, Birmingham B15 2TH, England) *Proc R Soc Med* 70(2): 111-112; 1977.

In 1950, during a review of scrotal epithelioma cases from the Birmingham, England, area, researchers considered some cases to be related to the use of cutting oils in automatic tool machines. Predictions of future increases have turned out to be correct. In 1971, a progressive increase was found in the number of registrations (morbidity in contrast to mortality) since 1950. This was in marked contrast to the pattern of deaths in England and Wales, which had shown a steady decline from the early 1940's. Occupational analysis showed an excess of toolsetters and automachinists. The findings indicate the carcinogenicity of the oil mist in factories where the men worked. In a study of 300 patients with scrotal cancer, an overall excess of observed over expected cases of subsequent primary tumors was found in three sites: the skin, respiratory tract, and upper alimentary tract. Thus, scrotal cancer is not only the product of a variety of different occupational carcinogens, but it can also act as a warning forerunner of occupational malignant disease at other sites. (11 refs.)

- 77-0121 **The Warburg Hypothesis Fifty Years Later.** (Eng.) Weinhouse, S. (Fels Res. Inst. and Dept. Biochemistry, Temple Univ. Sch. Medicine, Philadelphia, PA 19140) *Z Krebsforsch Klin Onkol* 87: 115-126; 1976.

The Warburg Hypothesis is reviewed 50 yr after it was proposed. Attempts to find the answer to cancer in alleged deficiencies of tumor mitochondrial functions, as based on studies with isolated organelles, should be tempered by the recognition that respiratory and associated mitochondrial functions are not impaired in the intact cells. Furthermore, the rapid and invasive proliferation of cancer cells is not compatible with an impairment of the major mechanisms of energy transduction. Studies have demonstrated the role of the citric acid cycle and the glycolytic enzymes in tumor respiration; however, there is no clear cut evidence for the special role of phosphofructokinase in the high aerobic and anaerobic glycolysis of tumors. It is not known whether the activity of pyruvate kinase isozyme is responsible for the high glycolytic activity of tumors other than Morris hepatomas. Since

glycolytic behavior is similar in both normal and cancer derived cultures, glycolysis cannot play a crucial role in malignant cell growth. A tumor growing in vivo is subject to hormonal and possible neural factors and may also be constrained in its metabolism by vascular flow and membrane transport. Therefore, mechanisms that operate in vitro to produce a Pasteur Effect are not necessarily working in vivo. Contrary to the Warburg Hypothesis, cultured cells invariably die if oxygen is rigidly excluded. It appears that high aerobic glycolysis is not necessarily an intrinsic property of the cancer cell, but rather an end result of a process of dedifferentiation; no single cause for high tumor glycolysis is known. (22 refs.)

77-0122 Similar Patterns of tRNA Structures and tRNA Methyltransferase in Embryonic and Tumor Tissue. (Eng.) Kuchino, Y. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 95-100; 1976.

Transfer RNA (tRNA) structures and tRNA methyltransferases in various tumor tissues were investigated, and the corresponding literature was reviewed. Every tumor tissue contained aberrantly hyperactive tRNA methylases; furthermore, the enzymes differed qualitatively from normal tissues. tRNA methylases were normal in benign tissues. An examination of tRNAs in Novikoff hepatoma indicated three tRNAs with greatly altered mobility: tyr-tRNA, his-tRNA and asn-tRNA. It is not clear whether these tumor specific tRNAs of normal tissue. The high excretion of tRNA breakdown components can be higher in some cancer patients than in normal subjects; an extremely labile population of tRNAs in tumor tissue has recently been discovered. The tRNA methyltransferase activity and the population of tRNAs from BeWo cells and normal human chorionic tissue were compared. The alterations demonstrated in other solid tumors were also found in the BeWo cells, indicating that these changes are part of the oncogenic process. A population of tRNA in embryonic and adult mouse liver and ascites cells in the same mouse line were also investigated. The phe-tRNA from the adult liver lacked one of the isoaccepting species present in embryonic tissue and the ascites cells. (16 refs.)

77-0123 Enzymology of Cancer Cells. (Eng.) Weber, G. (Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianapolis, IN 46202) *N Engl J Med* 296(9): 486-493; 1977.

The relevant quantitative and qualitative differences in the enzymology of the cancer cell that distinguish it from normal cells were integrated. Not all enzymes should be expected to be linked to transformation and progression, because integration of gene expression operates through the control of a rela-

tively small number of key enzymes. The key enzymes are so termed because the regulation of the rate and direction of the flux of opposing and competing synthetic and catabolic pathways is achieved through control of these enzymes. In contrast, there are a number of enzymes that are not key enzymes, because they do not become limiting. Key enzymes in de novo and salvage processes of pyrimidine and DNA biosynthesis increase and the opposing catabolic enzymes decrease in parallel with tumor growth rate. As a result, a progressive imbalance emerges between the activities of the synthetic and catabolic enzymes and between the overall activities of the opposing pathways of anabolism and catabolism. Since the activities of the key enzymes and opposing metabolic pathways correlate with tumor growth rate, these alterations are progression-linked manifestations of the reprogramming of gene expression in neoplasia. The enzymes with the lowest activities in the normal adult rat liver increase to the highest extent in the most rapidly growing hepatomas. On the other hand, the synthetic enzymes with the greatest activity in normal liver have the smallest extent of rise in the rapidly growing neoplasms. The transformation- and progression-linked imbalance in pyrimidine and DNA metabolism provides an increased synthetic capacity for the tumor cells and a sharply curtailed catabolic potential, conferring selective advantages on the cancer cells. The integrated pattern of imbalance in pyrimidine and DNA metabolism indicates key enzymes as targets for chemotherapy. (57 refs.)

77-0124 Enzymology of Cancer Cells (Second of Two Parts). (Eng.) Weber, G. (Lab. Experimental Oncology, Indiana Univ. Sch. Medicine, Indianapolis IN 46202) *N Engl J Med* 296(10): 541-551; 1977.

In carbohydrate metabolism, key glycolytic enzymes increase, and the opposing gluconeogenic ones decrease, parallel with the rate of hepatoma growth. Qualitative changes are manifested in an isozyme shift, which indicates a reprogramming of gene expression. In ribose-5-phosphate metabolism, increased activities of glucose-6-phosphate dehydrogenase, transaldolase, and transketolase can channel the glycolytic intermediates into pentose phosphate biosynthesis. The activity of phosphoribosylpyrophosphate (PRPP) synthetase routes this pentose into increased PRPP synthesis. Activities of the following key enzymes involved in liver purine metabolism and inosinic acid (IMP) synthesis are increased in hepatomas: glutamine PRPP amidotransferase, adenylosuccinase, adenylosuccinate synthetase, AMP deaminase, and IMP dehydrogenase. In contrast, catabolic enzyme activity is decreased. This integrated pattern of imbalance provides the tumor cell with an increased capacity for purine biosynthesis. Transformation- and progression-linked alterations in key enzyme activities are summarized. Such markers of malignant transformation found in chemically induced hepatomas in rats may be applicable to human hepatomas and hypernephromas. Key enzymes linked with neoplastic transformation behave in an orderly pattern, whereas random alterations in non-key enzymes do not correlate with malignancy.

nancy. Thus, key enzymes would be the preferred target for chemotherapy. (72 refs.)

- 77-0125 **Temperature-Sensitive Mutations in Animal Cells.** (Eng.) Basilico, C. (Dept. Pathology, New York Univ. Sch. Medicine, New York, NY) *Adv Cancer Res* 24: 223-266; 1977.

Temperature-sensitive (ts) mutants of animal cells can be obtained with reasonable frequency. The mutants are stable and homogeneous, with a low reversion frequency. A review is presented of the following aspects of ts mutations: methods of induction and selection, frequency and general behavior, characterization, and genetic analysis. The characteristics of some ts growth mutants are tabulated. Particular discussion is made of cell lines with ts mutations that affect the expression of specialized functions and in vitro transformation properties. Ts mutations are recessive: the development of methods provoking monosomies or chromosomal deletions should thus be of great advantage in increasing the yield of ts mutants. (90 refs.)

- 77-0126 **The Use of the Human Leukocyte Test System for the Evaluation of Potential Mutagens.** (Eng.) Obe, G.; Beek, B.; Slacik-Erben, R. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the Meeting Held at Montpellier, June 1975.* The European Society of Toxicology (New York: American Elsevier Publishing Co., Inc.): pp. 118-127; 1975.

A discussion of the human leukocyte test system as the most practical method for the evaluation of mutagenic damage in man is presented. Cytogenic tests can be carried out either in vitro by treating culture cells with an agent or in vivo by culturing cells from persons exposed to an agent and analyzing the mitoses. Cells are grown in Ham's F-10 or TC medium 199 cultures. The lymphocytes are induced to enter the autotrophic cell cycle in vitro by means of an antigenic trigger; phytohemagglutinin from *Phaseolus vulgaris* is frequently used. In Ham's F-10 cultures, DNA synthesis begins about 26 hr after culture initiation, and the first mitoses occur at about 34 hr. Two subpopulations of cells are demonstrated by two peaks of DNA synthesis occurring between 34 and 44 hr and by two peaks of mitoses between 40 and 50 hr. In TC medium 199 cultures, the first mitoses are seen at about the same time as in Ham's cultures, but they are infrequent. At 50 hr, more mitoses occur, corresponding to the second subpopulation in Ham's medium. Subpopulations cannot be detected from the mitotic indices in TC medium 199 cultures. For in vivo investigations the 2-day Ham's F-10 culture is preferred. Factors that influence the outcome of results with the leukocyte system include different sensitivities of subpopulations of cells against mutagens, selection, origin of spontaneous aberrations in vitro, inter- and intra-individual differences in spontaneous aberration rates, and cell cycle delaying effects. (58 refs.)

- 77-0127 **Intracellular Membranes and Posttranscriptional Regulation in Liver and Hepatoma.** (Eng.) Pitot, H. C.; Cardelli, J.; Long, B.; McLaughlin, C. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy.* Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 329-342; 1976.

The mechanisms of translation, ie, protein synthesis by ribosomes on messenger RNA (mRNA), in eukaryotic cells are discussed together with the effects of membrane-bound polyribosomes on translation. The three functions of these polysomes are protein secretion, segregation, and mRNA stabilization. Although all have a regulatory role in translation, only mRNA stabilization directly influences the cell phenotype. Studies of this function show that the lifetimes of mRNA's for certain hepatoma enzymes differ from those of liver mRNA's. In contrast, normal differentiation exhibits a pattern of template stabilization coincident with the development of the tissue involved. The data suggest that variations in template stability are characteristic of neoplastic transformation. A model of a functioning membrane-bound polysome is presented that predicts that polysomes synthesizing organ-specific proteins bind only to the endoplasmic reticulum of that organ. (63 refs.)

- 77-0128 **Action of Adenosine 3', 5'-Phosphate in Chinese Hamster Ovary Cells.** (Eng.) Hsie, A. W.; O'Neill, J. P.; Schroder, C. H.; Kawashima, K.; Borman, L. S.; Li, A. P. In: *Control Mechanisms in Cancer. Progress in Cancer Research and Therapy.* Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): vol. 1, pp. 183-203; 1976.

Experiments demonstrating that cyclic AMP (cAMP) may regulate mammalian cell growth are summarized. Epithelial-shaped Chinese hamster embryo (CHO) cells growing in a compact multilayered colony were transformed into a contact-inhibited monolayer of elongated, fibroblastlike cells when treated with N^6, O^2' -dibutryl cAMP (Bt_2cAMP). The morphological conversion was accompanied by the disappearance of cell-surface knobs, a decrease in cell agglutinability, an increase in the number of microtubules, and the induction of collagen synthesis. When the CHO cells were continuously exposed to Bt_2cAMP , morphological transformation occurred only in cells in the G_1 phase. Hormones such as testosterone and prostaglandins acted synergistically with Bt_2cAMP . The effect of Bt_2cAMP on cell morphology was due to an increase in endogenous cAMP levels, presumably as a result of the competitive inhibition of cAMP phosphodiesterase by accumulated intracellular N^6 -monobutryl cAMP. The cytoplasmic protein kinase activity of cells treated with Bt_2cAMP , cholera toxin, or prostaglandin E_1 was activated in vivo, resulting in the conversion of cAMP-sensitive protein kinase to cAMP-independent subunits. This activation may be involved in the observed morphological transformation. Although the mechanisms of morphological transformation are obscure, cAMP, alone or in combination with certain hormones, may have an important role in regulating the morphology and growth of all mammalian cells. (36 refs.)

77-0129 Cyclic Nucleotides in Normal and Transformed Fibroblasts. (Eng.) Johnson, G. S. *In: Control Mechanisms in Cancer* Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Progress in Cancer Research and Therapy vol. 1, pp. 153-160; 1976.

Recent results of studies with cyclic nucleotides are reviewed. Cyclic nucleotides play an important role in growth control mechanisms. The addition of cyclic AMP N⁶, O^{2'}-dibutyl cyclic AMP (Bt₂cAMP) to cultures of transformed cells induced cell elongation and made the cells appear more normal. BHK cells grew more rapidly and had lower cyclic AMP

levels when insulin was added to the culture media. Transformed cells differ from their parent normal cells in many respects. The addition of cyclic AMP analogue changes many of these properties so that phenotypically the cells resemble normal cells. Studies indicate that the abnormalities in transformed cells were caused by decreased cyclic AMP levels. The molecular basis for this decrease in cyclic AMP activity was an alteration of adenylate cyclase in the transformed cells. Cells at confluency showed correspondingly higher levels of cyclic AMP. The role of cyclic GMP in growth or transformation remains unclear. (25 refs.)

CHEMICAL CARCINOGENESIS

77-0130 Asbestos Spraying, an Occupational and Environmental Hazard. (Eng.) Barnes, R. (Port Stephens Care Centre, Gowrie Ave. and Kerrigan St., Nelson Bay, New South Wales 2315, Australia) *Med J Aust* 2(16): 599-602; 1976.

The potential danger of asbestos spraying is illustrated by the case histories of three men who had not faithfully worn a mask while working. The first is that of a 33-yr-old man who had been a spray operator for 10 yr. He had been in good health until 5 yr previously, when he felt tired and dyspneic. He had a small hemoptysis 4 1/2 yr later, and, upon examination, a left-sided pleural effusion was found. Biopsy of the lung revealed asbestos bodies. The x-ray report was linear fibrosis with pleural thickening in the lower zones, suggesting asbestosis. A second operator had been employed in the industry for less than 3 yr, more than 7 yr previously. His main complaints were a 7-mo history of left-sided pleuritic chest pain, exertional dyspnea, and a dry cough. On examination, crepitations at both lung bases and in the right axilla were heard. The x-ray report was micronodular fibrosis over approx one-third of the lung fields, pleural thickening at the bases, and linear fibrosis. The third case is that of a 60-yr-old man had worked as an operator for 7 yr, over a 15-yr period. He complained of dyspnea on effort for the last 7 yr. On examination of the patient's chest, pronounced basal and axillary crepitations were heard. Early finger clubbing was present. There was no improvement with a bronchodilator. The radiologist's report on an x-ray film was micronodular fibrosis of two-thirds of his lung fields and extensive pleural thickening and calcification over both lung fields. Asbestos fiber counts as high as 150 million particles/cubic foot have been registered in the vicinity of sprayers. Asbestos linings of buildings should be replaced by less-dangerous materials. (6 refs.)

77-0131 Breast Cancer and Use of Rauwolfia and Other Antihypertensive Agents in Hypertensive Patients: a Nationwide Case-Control Study in Finland. (Eng.) Aromaa, A. (Res. Inst. for Social Security, Social Insurance Inst. Finland, Pohjoinen Hesperiankatu 15 A, SF-00260, Helsinki 26, Finland) Hakama, M.; Hakulienn, T.; Saxen, E.; Teppo, L.; Idanpaan-Heikkila, J. *Int J Cancer* 18(6): 727-738; 1976.

The relationship, if any, between breast cancer and the use of rauwolfia and other antihypertensive agents in hypertensive patients was studied in Finland. Rauwolfia was the main antihypertensive agent used in 48 cases and 48 controls, methyldopa in 41 cases and 39 controls, another antihypertensive agent (not specified) in 11 cases and 12 controls, and a diuretic in 9 cases and 10 controls. All relative risks were between 0.90 and 1.11 when classification was based on the main antihypertensive agent used. In all, there was no indication of any association between risk of breast cancer and use

of rauwolfia, methyldopa, other antihypertensive agents, or a diuretic as main antihypertensive medication. The relative risk of breast cancer in rauwolfia users versus nonusers was slightly raised, from 1.00 to 1.30, and the risk associated with any amount of rauwolfia from 1.16 to 2.14. However, the association was not statistically significant. No new associations of breast cancer with the use of other antihypertensive agents emerged. To eliminate any possible complication due to the association of heart disease and breast cancer, pairs (cases or controls) that used digitalis were excluded. With the exception of two relative risks for methyldopa, the observed relative risks were below unity. It is unlikely that the use of rauwolfia elevates the risk of breast cancer. (25 refs.)

77-0132 The Effect of Perphenazine Treatment on Testosterone Metabolism by Established Rat Mammary Carcinomas. (Eng.) Buchan, P. (Dept. Clinical Surgery, Medical Sch., Univ. Edinburgh, Edinburgh EH8 9AG, Scotland, United Kingdom) Fraser, A. T.; Miller, W. R. *Biochem Soc Trans* 4(6) 1100-1102; 1976.

The influence of perphenazine treatment on testosterone metabolism by established rat mammary carcinomas was studied. Tumors induced in female Sprague-Dawley rats by intragastric administration of dimethylbenzanthracene (30 mg in cotton-seed oil) at 50 days of age were measured three times weekly by calipers. Animals bearing tumors that showed continuous growth were allocated to treatment or control groups when the tumor size was approx 1.5 x 1.5 cm. The treatment group received daily sc injections of perphenazine (5 mg/kg) until sacrifice 12 days later. Testosterone metabolism in vitro was determined in 10 tumors from each group. Tumors from the treated animals showed a significantly higher metabolism of testosterone than those from controls. The major metabolites of testosterone in tumors from the two groups of animals were 5 α -dihydrotestosterone and 5 α -androstenediol. However, the conversion into both metabolites was significantly higher in tumors from the perphenazine-treated group. The increase in 5 α -reduction alone accounted for the higher concentrations of testosterone metabolized. All but one of the tumors from the treated group demonstrated an acceleration of growth during the treatment period, whereas those from control animals showed no significant change. It is concluded that short-term administration of perphenazine stimulates tumor growth and testosterone metabolism in dimethylbenzanthracene-induced rat mammary carcinomas. (5 refs.)

77-0133 Effect of Treatment with Estrogen Conjugates on Endogenous Plasma Steroids. (Eng.) Rose, D. P. (Div. Clinical Oncology, Univ. Hosps., Madison, WI 53706) Fern, M.; Liskowski, L.; Milbrath, J. R. *Obstet Gynecol* 49(1): 80-82; 1977.

The influence of treatment with estrogen conjugates on en-

ogenous plasma steroids was investigated. The 160 controls comprised 68 postmenopausal women and 92 premenopausal women; none had received any form of steroid therapy for at least 6 mo. An age-matched (52 ± 5 yr) subgroup was used for direct comparison with 61 estrogen-treated women. All of the latter (aged 40-66 yr) were taking conjugated estrogens (Premarin) in daily doses of 0.625, 1.25, or 2.5 mg. Plasma dehydroepiandrosterone sulfate, androstenedione, and estrone plus estradiol levels were significantly lower in postmenopausal controls compared with premenopausal controls, but in both groups plasma estril levels were below the sensitivity of the assay. Furthermore, plasma dehydroepiandrosterone sulfate and androstenedione were negatively correlated with age; this factor was independent of menopausal status, being evident within the premenopausal group and, in the case of androstenedione, within the postmenopausal women. Estrogen therapy had no discernible effect on the plasma levels of dehydroepiandrosterone sulfate or androstenedione. When taken in doses of 2.5 or 1.25 mg, but not 0.625 mg, the estrogen conjugates produced significant elevations in plasma estrone plus estradiol compared with control values; the concentrations were similar to those seen in premenopausal women. Plasma estril was readily assayable in the estrogen-treated groups and represented 26% of the total plasma estrogens in women receiving 0.625 mg daily, 16% in those receiving 1.25 mg and 18% in those taking 2.5 mg. At the lowest dose, 16 α -hydroxylase, activity was sufficient for the exogenous estrogens to be mainly metabolized to estril. (17 refs.)

77-0134 Carcinogenic Action of Diethylstilbestrol on Frogs. (Eng.) Khudolei, V. V. (Lab. Chemical Carcinogenic Agents, N. N. Petrov Res. Inst. Oncology, Ministry Health USSR, Leningrad, USSR) *Exp Biol Med* 81(6): 998-900; 1976.

The action of diethylstilbestrol propionate (DES) was evaluated in 46 female and 52 male frogs (*Rana temporaria*) aged 1-1.5 yr. The animals received DES injections of 40-200 μ g/wk sc in the dorsal region. Well-developed large-droplet fatty degeneration was observed in the kidneys and, especially, in the liver, accompanied by the presence of large cysts filled with fat. In 6/21 females and 2/17 males surviving > 9.5 wk, neoplasms of the hematopoietic tissue (7 cases) and liver (2 cases) were discovered. The av latent period of tumor development was 15.6 wk. The minimal dose of DES causing tumor development was 480 μ g, and the max dose was 4,400 μ g. Neoplastic changes of the hematopoietic system were classified as hemocytoblastosis. They consisted of multiple foci of proliferation composed of small, atypical basophilic cells generally arranged among the blood vessels in the liver, kidneys, and spleen. Against the background of these severe degenerative changes in the liver, an undifferentiated invasive hepatocellular carcinoma developed. A high degree of polynormorphism was noted, with pathological mitoses in some cells. No metastases or neoplasms in other sites, including the pituitary gland, were observed. In control frogs (11 females, 5 males) receiving vegetable oil only, no tumors were found.

These experiments demonstrate for the first time that DES has a carcinogenic action on amphibians, and they reveal great sensitivity of these animals to large doses of the estrogen. (7 refs.)

77-0135 Hormone Replacement Therapy and Endometrial Carcinoma(Letter to Editor). (Eng.) Hutton, J. D. (Dept. Obstetrics Gynecology, Saint Mary's Hosp. Medical Sch., London W2, England) Murray, M. A.; Jacobs, H. S.; Beard, R. W.; James, V. H. *Lancet* 1(8014): 745-746; 1977.

In this reply to an editorial about the relation between endometrial cancer and estrogen treatment of postmenopausal women, the question is raised whether it is the type or the amount of exogenous estrogen that determines if undesirable changes occur in the endometrium. When estrone sulfate (as 1.5 mg of the piperazine salt Harmogen) is given, there is a four- to fivefold increase of the plasma concentration of unconjugated estrone and a two- to threefold increase of unconjugated estradiol. These concentrations are similar to those observed after ingestion of estradiol (as 2 mg of the valerate Progy Nova). The preferential increase of plasma estrone concentrations after ingestion of estradiol valerate is similar to that produced by po micronized estradiol-17 β . It is thought to be caused by oxidation of estradiol. These data emphasize that biochemical differences between certain hormone preparations may be more apparent than real. The adjectives "natural" and "synthetic", when applied to preparations used to treat postmenopausal women, are frequently more ambiguous than helpful. (5 refs.)

77-0136 The Role of Prolactin in Breast Cancer. (Eng.) Friesen, H. G. (Dept. Physiology, Univ. Manitoba, Winnipeg, Canada) *Rec Results Cancer Res* 57: 143-149; 1976.

Prolactin has a major role in development of mammary tumors in animals. In humans, the evidence is less convincing. A study of 68 human mammary tumors and 20 benign lesions is reviewed. About 60% of the malignant tumors had sites for estrogen; of these, 20% bound prolactin, 85% bound insulin, and 4% bound growth hormone. (20 refs.)

77-0137 DNA Binding and Its Relationship to Carcinogenesis by Different Polycyclic Hydrocarbons. (Eng.) Huberman, E. (Dept. Genetics, Weizmann Inst. Science, Rehovoth, Israel) *Int J Cancer* 19(1): 122-127; 1977.

Five polycyclic hydrocarbons with different degrees of carcinogenicity in vivo were tested for their metabolism to water-soluble products and their binding to DNA, RNA and protein in normal embryonic hamster and baby hamster kidney (BHK) cells. The compounds studied were 7,12,- dimethylbenz(a)anthracene, benzo(a)pyrene; 20-methylcholanthrene, dibenz(a,h)anthracene and dibenz(a,c)anthracene, each was added at 10 μ M. All five compounds were metabolized to water-soluble products in

both types of cells and treatment of cells with aminophylline (0.1 mM, beginning 2 hr before the addition of hydrocarbon) enhanced this metabolism. After and not before this enhancement of metabolism by aminophylline, binding of the hydrocarbon to DNA was positively correlated with the carcinogenicity of that hydrocarbon. There was no such relationship with binding to RNA or protein. The results suggest that DNA is the target for carcinogenesis by such carcinogens. (21 refs.)

- 77-0138 Metabolism of Benzo[a]pyrene. Effect of 3-Methylcholanthrene Pretreatment on Metabolism by Microsomes from Lungs of Genetically "Responsive" and "Nonresponsive" Mice.** (Eng.) Seifried, H. E. (Natl. Inst. Arthritis, Metabolism, Digestive Diseases, NIH, Bethesda, MD 20014) Birkett, D. J.; Levin, W.; Lu, A. Y.; Conney, A. H.; Jerina, D. M. *Arch Biochem Biophys* 178(1): 256-263; 1977.

The metabolism of ^{14}C -benzo[a]pyrene (BP) by microsomes from the lungs of normal and 3-methylcholanthrene (3-MC)-treated DBA/2J, C57BL/6J, and A/HeJ mouse strains was investigated by high-pressure liquid chromatography (HPLC). The specific activities (picomoles of BP metabolized per milligram of protein per minute) of lung microsomes from the strains were significantly induced by treating the animals with 3-MC. Strains C57BL/6J and DBA/2J were induced 20-fold, and strain A/HeJ was induced over 50-fold. The specific activity of the constitutive enzymes in strain C57BL/6J was twice that for the other two strains. After induction by 3-MC, the specific activity for A/HeJ was almost three x that for strain DBA/2J. The percentages of the various metabolite fractions produced by lung microsome from 3-MC-treated animals were almost identical in all three strains. Metabolism profiles for the control lung enzymes, however, showed some strain differences. C57BL/6J and A/HeJ mice formed twice as much dihydrodiols as a percentage of total metabolism compared to DBA/2J mice. DBA/2J mice produced less phenol 2 fraction and significantly more quinones than C57BL/6J and A/HeJ mice. Treatment of DBA/2J mice with 3-MC resulted in a more selective induction of all three dihydrodiol fractions as well as the phenol 2 fraction. Quinone 1 and, especially, quinone 2 fractions were selectively decreased as a percentage of total BP metabolism upon treatment of DBA/2J mice with 3-MC. In these strains of mice, the most striking difference between metabolism in liver microsomes (observed previously) compared to lung microsomes was a threefold increase in total dihydrodiols as a percentage of total metabolites formed. (25 refs.)

- 77-0139 Benzo(a)pyrene Metabolism by Isolated Rat Intestinal Epithelial Cells.** (Eng.) Stohs, S. J. (Dept. Forensic Medicine, Karolinska Institutet, Stockholm, Sweden) Grafstrom, R. C.; Burke, M. D.; Orrenius, S. *Arch Biochem Biophys* 179(1): 71-80; 1977.

The metabolism of benzo(a)pyrene (BP) by male Sprague-Dawley rat intestinal epithelial cells isolated using collage-

nase plus hyaluronidase was examined. BP hydroxylation was linear with cell concentrations up to 1×10^6 cells/ml from 3-methylcholanthrene (MC)-treated rats and up to 3×10^6 cells/ml from control rats. At all cell concentrations, the cells from MC-treated rats were approx 30x more active than the control cells. The hydroxylation rate was linear for approx 8 min with both control and MC-induced cells. At 1 to 2 mM salicylamide, a 30% increase in the accumulation of hydroxylated BP products occurred with both cell types. At concentrations > 2.5 mM salicylamide, accumulation of the fluorescent hydroxylated products of BP decreased. The inhibitory effects of metyrapone, SKF 525-A, rotenone, and α -naphthoflavone (α -NF) on BP metabolism in intestinal cells from MC-treated rats were determined. α -NF was the most potent compound, producing 68% inhibition at a 250 μM concentration. SKF 525-A was a more potent inhibitor of BP metabolism than metyrapone. Rotenone was least inhibitory at the higher concentrations, but at concentrations < 50 μM , it was as inhibitory as α -NF. There was a large increase in BP-dihydrodiols between 5 and 30 min either with or without salicylamide present. The amount of quinones did not increase greatly over 30 min in the absence of salicylamide, but it did increase when salicylamide was present. Similar behavior was observed with the metabolites BP 4,5-oxide and 3-hydroxy BP. 9-Hydroxy BP increased significantly, even in the absence of salicylamide, although it increased more with salicylamide present. The pattern of organic-soluble BP metabolites differed after 30 and 5 min of incubation. After 5 min, BP 4,5-oxide and 3-hydroxy BP comprised the majority of metabolites, with hardly any dihydrodiols; after 30 min, in the absence of salicylamide, the dihydrodiols and 9-hydroxy BP were the major metabolites, at the expense of the oxide and 3-hydroxy BP. Subsequent hydrolysis with aryl sulfatase usually did not alter the overall percentage distribution pattern of the metabolites. Hydrolysis with β -glucuronidase resulted primarily in a percentage increase in 3-hydroxy-BP. Intestinal cells offer a convenient method of studying intestinal drug metabolizing processes that may significantly contribute to the overall xenobiotic metabolism in the body. (35 refs.)

- 77-0140 Benzo[a]pyrene 7,8-Dihydrodiol Is More Carcinogenic than Benzo[a]pyrene in Newborn Mice.** (Eng.) Kapitulnik, J. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Incorporated, Nutley, NJ 07110) Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M. *Nature* 266: 378-380; 1977.

The carcinogenicity of benzo(a)pyrene (BP) and benzo(a)pyrene 7,8-dihydrodiol was studied in newborn mice. BP and BP 7,8-dihydrodiol were dissolved in anhydrous dimethyl sulfoxide (DMSO) at a final concentration of 200 nanomoles (nmol)/5 μ . The compounds were injected ip into newborn mice as follows: 200 nmol on the first day of life, 400 nmol 1 wk later, and 800 nmol at 15 days of age. Control animals were given 5, 10, and 20 μ of DMSO using the same schedule. Large differences in survival among the animals did not occur until they were 25 days of age. The experiments lasted 21-24 wk. A complete histopathological examination was per-

formed on most animals. Among the BP 7,8-dihydrodiol-treated animals that died and were autopsied between 4 and 17 wk of age, 31% had lung adenomas and 64% had malignant lymphomas; among those that died or were sacrificed at the age of 18-24 wk, 92% had lung adenomas and 75% had malignant lymphomas. BP-treated animals also developed lung adenomas, but the number per animal was much lower compared to BP 7,8-dihydrodiol-treated animals. Only 4% of the control animals developed pulmonary adenomas. It is concluded that BP 7,8-dihydrodiol is a more potent carcinogen than BP when injected into newborn mice and is, therefore, a proximate carcinogenic metabolite of BP. (20 refs.)

77-0141 Nucleoside Adducts from the In Vitro Reaction of Benzo[a]pyrene 4,5-Oxide with Nucleic Acids. (Eng.) Jennette, K. W. (Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY 10032) Jeffrey, A. M.; Blobstein, S. H.; Beland, F. A.; Harvey, R. G.; Weinstein, I. B. *Biochemistry* 16(5): 932-938; 1977.

The covalent binding of benzo(a)pyrene 4,5-oxide (BP 4,5-oxide) and benzo(a)pyrene-7,8-dihydrodiol 9,10-oxide (BP-7,8-dihydrodiol 9,10-oxide) isomers I and II to nucleic acids in aqueous acetone soln was investigated. BP 4,5-oxide reacted preferentially with guanosine residues, whereas BP-7,8-dihydrodiol 9,10-oxide isomers I and II reacted extensively with guanosine, adenosine, and cytidine residues. The rates of reaction with the different homopolyribonucleotides followed the order poly (G) > poly (A) > poly (C). Alkaline or enzymatic hydrolysis of the modified nucleic acids and subsequent chromatography of sephadex columns yielded BP-nucleotide adducts, which were converted enzymatically to the corresponding nucleosides. These, in turn, were resolved into several distinct components by high-pressure liquid chromatography (HPLC). Evidence was obtained for the presence of multiple nucleoside adducts of guanosine, adenosine, cytidine, deoxyguanosine, deoxyadenosine, and deoxycytidine. HPLC profiles of adducts formed with isomers I and II were different. The structural aspects of these nucleoside adducts are discussed. (48 refs.)

77-0142 The In Vitro Oxidative Metabolism of Benzo(a)pyrene in Human Liver Measured by Different Assays. (Eng.) Pelkonen, O. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, Bethesda, MD 20014) *Chem Biol Interact* 16(1): 13-21; 1977.

The metabolism of tritiated benzo(a)pyrene (BP) was studied in biopsied samples of adult human liver, and the metabolites were analyzed by thin layer chromatography (TLC). The metabolites included several dihydrodiols, phenols, and quinones. The production of particular metabolites by different individuals varied greatly, sometimes as much as twentyfold. Overall metabolism was inhibited by aminopyrine and SKF 525A, but not by 7,8-benzoflavone. Dihydrodiol formation

was inhibited by epoxide hydratase inhibitors such as styrene oxide and trichloropropene oxide. A correlation was observed between the activity of BP-hydroxylase measured fluorometrically and the production of phenols, total dihydrodiols, and individual dihydrodiols estimated by radioactivity counting after separation by TLC. (38 refs.)

77-0143 Michaelis-Menten Kinetic Analysis of the Hepatic Microsomal Benzpyrene Hydroxylase from Control, Phenobarbital- and Methyl-3-cholanthrene-Treated Rats. (Eng.) Cumps, J. (Unite de Chimie Therapeutique, Louvain Pharmacy Sch., Louvain, Belgium) Razzouk, C.; Roberfroid, M. B. *Chem Biol Interact* 16(1): 23-38; 1977.

An extensive study was made of the kinetics of the rat liver microsomal enzyme, benzpyrene hydroxylase. Michaelis-Menten kinetics were obeyed only at very low microsome concentrations (< 6 μg protein/ml). At higher concentrations, the K_m of the reaction increased with increasing microsome concentrations. This was found to be a consequence of reversible nonspecific substrate binding. Pretreatment of the rats with 3-methylcholanthrene decreased the K_s value of the reaction from 2.48 to 0.23×10^{-6} M, but had no effect on V_{max} ; conversely, pretreatment with phenobarbital decreased V_{max} but did not affect K_s . (40 refs.)

77-0144 Capacity of Cultured Cells to Accumulate Polycyclic Hydrocarbons in Microspectrofluorometrically Detectable Quantities. Preliminary Results. (Fre.) Salmon, J. M. (Laboratoire de Chimie Physique, Centre Universitaire, Avenue de Villeneuve, 66025 Perpignan, France) Viallet, P.; Kohen, E.; Zajdela, F. *INSERM Symposia Series* 52(13): 253-260; 1976.

The experimental conditions required for a quantitative detection of trace amounts of aromatic hydrocarbons were studied. The requirement for a recording of the complete fluorescence emission spectrum is emphasized as a condition for quantitative results. Observations effectively made on fluorescence emission spectra recorded from cells grown in the presence of traces of BP are reported. The cells selected for this type of studies should exhibit a relatively slow metabolism of the hydrocarbon. In most cases, the fluorescence spectrum recorded from benzo(a)pyrene (BP)-medium grown cells was not identical to that of BP soln (less defined structure, displaced maxima, and modified relative intensities of maxima). The spectrum observed in the BP medium grown cells is apparently the result of two spectra, one corresponding to a free BP fraction, the other to a BP fraction interacting with cellular constituents. When the cells were maintained for periods up to 1 to 3 mo with low amounts of BP, the BP fractions "interacting" seemed relatively more significant than in cells not "adapted" to BP. The quantitative determination of the hydrocarbon in the living cell can be achieved only after definition of a sufficiently precise experimental protocol. (7 refs.)

77-0145 Determination of 3,4-Benzopyrene Content in Seeds Before and After Germination. (Ger.)

Wettig, K. (Lehrstuhl Allgemeine und Kommunale Hygiene, Hygiene-Institut der Humboldt-Universität, Otto-Grotewohl-Str. 1, DDR-108 Berlin, E. Germany) Chesina, A. J.; Gelbert, G.; Schabad, L. M. *Arch Geschwulstforsch* 46(8): 634-638; 1976.

The 3,4-benzopyrene content of commercial seeds was determined before and after germination. Bush bean, pea, dill, spinach, lupine, and *Lepidium sativum* L. seeds were germinated in a carbon-free nutrient solution. The 3,4-benzopyrene content was considerably lower after germination than before, ie, there was no endogenous 3,4-formation during germination. Rye, oat, and pea seeds were germinated in nutrient solutions containing sodium acetate as a source of carbon. The 3,4-benzopyrene contents were higher after germination than before, indicating 3,4-benzopyrene synthesis. No correlation was found between the rate of increase of 3,4-benzopyrene and the concentration of the acetate in the nutrient solution. (17 refs.)

77-0146 Phorbol Myristate Acetate: A Mitogen Selective for a T-Lymphocyte Subpopulation. (Eng.)

Touraine, J. L. (Lab. Immunopharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Hadden, J. W.; Touraine, F.; Hadden, E. M.; Estense, R.; Good, R. A. *J Exp Med* 145(2): 460-465; 1977.

Phorbol myristate acetate (PMA), a potent mitogen for human peripheral blood lymphocytes (PBL) which potentiates the action of carcinogens in inducing epidermoid tumors of mouse skin, was investigated in terms of its possible effects on lymphocytes in order to obtain information on the role of immune responses in epidermal carcinogenesis. Maximal stimulation of human PBL was observed at a PMA concentration of 100 nanograms (ng)/ml and occurred at 4 to 5 days of culture. Comparable responses were observed for phytohemagglutinin (PHA) at a concentration of 3 μ g/ml, with the max response occurring at 3 days of culture. In 11 experiments directly comparing PHA (3 μ g/ml) and PMA (100 ng/ml) at 72 hr of culture, the incorporation of ³H-thymidine by human PBL was $280 \pm 24 \times 10^3$ cpm/culture and $234 \pm 26 \times 10^3$ cpm/culture, respectively. There was, however, great variations in the relative responses. Stimulation by PMA was greater than that of PHA in 5 of 11 individuals, suggesting that PMA and PHA might be acting on different lymphoid populations. To further compare the response of lymphocytes to PHA and PMA, a 5'-bromodeoxyuridine and light technique was used to ablate the cells proliferating in response to stimulation by each of the mitogens. When the PHA response was ablated, the PMA response was unaffected; similarly if the PMA response was ablated, the PHA response was left unaffected. Experiments performed to subclassify lymphocytes by rosetting with sheep RBC revealed that the PMA response resides almost exclusively with the rosetted population. In a further experiment with a single rosette sedimentation which removed only those T lymphocytes with a high

affinity for sheep RBC (one-third to one-half of the total T lymphocytes), only 1% of the response to PMA occurred in the non-rosette-forming cell population in contrast to 60%, 45%, and 68% for the responses to PHA, concanavalin A, and pokeweed mitogen. Thus, PMA appears to be mitogenic for a subpopulation of thymus-derived lymphocytes having a relatively high affinity for sheep RBC and different from those responsive to PHA. (18 refs.)

77-0147 Studies on Biological Characterization of Mammary Tumors of the Sprague-Dawley Rat in the Syngeneic Tumor-Host System. I. Spontaneous Primary Mammary Tumors and Tumors Induced by Oral and Intravenous Application of DMBA. (Ger.) Nowak, C. (Zentralinstitut für Krebsforschung der AdW der DDR, DDR-1115 Berlin-Buch, Lindenberger Weg 80, E. Germany) Arnold, W.; Mehnert, W. H. *Arch Geschwulstforsch* 46(7): 549-554; 1976.

Spontaneous and dimethylbenzanthracene (DMBA)-induced tumors in inbred Sprague-Dawley rats are discussed. The incidence of spontaneous tumors was 14.3% and that of chemically-induced tumors was 43.6%. Five different methods of chemical application were tested. Intravenous application was superior to po application with regard to dose, mortality and tumor incidence. DMBA induced 87.2% of the carcinomas and 12.8% of the benign tumors in the mammary glands. (14 refs.)

77-0148 In Vitro Malignant Transformation of Cells of Whole Embryos, Fetal Brain, and Newborn Lungs of Hamsters (Meeting Abstract). (Fre.) Levy, S. (Fondation Curie-Institut du Radium, Section de Biologie, 26 rue d'Ulm, 75 231 Paris cedex 05, France) Markovits, P.; Beesau, O.; Benda, P. *J Microsc (Paris)* 27(1): 17a; 1976. (no refs.)**77-0149 Pyridine and Adenine Nucleotide Ratios and Futile Substrate Cycling in Regulation of Energy Metabolism and Proposed Hyperthermic Regression of Neoplasms. (Eng.)** Williams, J. F.; Cook, P. C.; Matthaei, K. I.; Halley, J. B. S. In: *Control Mechanisms in Cancer*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. Progress in Cancer Research and Therapy. (New York: Raven Press): Vol. 1, pp. 425-439; 1976.

Differences in metabolic and morphologic behavior between a neoplasm and its normal parent tissue are described. The time course of 3'-methyl-4-N-dimethylaminoazobenzene (MDAB) tumorigenesis was studied in male Wistar rats; the rats, 150-200 g, were constantly given the carcinogen from age 10 wk at the level of 0.06% of the solid diet for 100 days. The carcinogen then was removed, and the rats maintained on normal rat chow. After 28 days of MDAB feeding, the livers appeared granular and showed moderate variegation with the greatest abnormality represented by depressed areas

of the capsule. In some livers, portal triads were evident, and there was mitotic activity in the cells associated with these triads. A few small tumors of the bile duct were present. After 84 days of MDAB treatment, the livers varied significantly from one animal to another. Parenchymal changes were manifested in the relative orientation of the centrilobular veins to each other. The distribution of Kupffer cells persisted in normal fashion. After 100 days of MDAB followed by 40 days of normal diet, the livers were plainly neoplastic. Large tumors were formed by the confluence of bile duct cell aggregates around small tumors to produce bile duct cell tumors and tumors of mixed cellularity. Some hepatocytes showed proliferative nodules and were devoid of glycogen. After 100 days of MDAB followed by 140 days of normal diet, the lesions varied from fibrotic hepatocellular tumors lacking malignant features to invasive necrotic tumors with residual marginal growth involving the adherent omental tissue and vascular permeation with tumors of malignant appearance. Increased glycolysis, along with increased lactate production, was observed across the time course of the development of the induced tumors. Hyperthermia at 42 C caused increased futile substrate cycling at the phosphofructokinase-fructose 1,6-diphosphate site, which might dissipate the reserves of ATP and the systems for ATP production and turnover, thus resulting in the removal of a portion of the energy component of the cell necessary for tumor growth. (34 refs.)

77-0150 Early Cytological Changes Induced in Rat Liver Cells by Chemicals. (Eng.) Masahito, P.; Takayama, S.; Yamada, K. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 103-111; 1976.

Cytogenetic studies on the effect of seven hepatocarcinogens—dimethylaminoazobenzene, DAB; 3'-methyl-DAB; 2-methylaminofluorene, 2-AAF; 2,7-AAF; aflatoxin B₁; α -benzene hexachloride; diethylnitrosamine and seven non-hepatocarcinogens (N-nitrosobutylurea; 2-Me-DAB; methionine; maleic hydrazide; DDT; furylfuramide cigarette tar) rat liver mitosis are reviewed. Male Donryu rats (8 wk old, 150 g) were given the compounds in the diet or drinking water for 3 wk. They were killed 3, 7, and 11 wk after the start of the treatment, and the liver tissue was examined microscopically. Mitotic rates in the livers of rats treated with the hepatocarcinogens were 10 times higher than those in controls (0.02%) after 3 wk, but they decreased to 0.05% after 11 wk. Except for N-nitrosobutylurea, which caused a slight increase, the nonhepatocarcinogens had no effect on mitosis. Rats sacrificed shortly after hepatocarcinogen treatment, other than with α -BHC over 95% of the dividing cells were diploid, the remainder being tetraploid; in the α -BHC rats, 90% of these cells were tetraploid. Nonhepatocarcinogens generally increased the proportion of tetraploid cells. However, after 11 wk, the frequency of diploid cells was about 90%, regardless of the compound administered. Chromosome

aberrations observed in liver cells in rats treated with hepatocarcinogens were mostly chromatid breaks and monocentric markers due to translocation between two chromosomes. In rats treated with nonhepatocarcinogens, mostly chromatid breaks occurred. These increased mitotic rates, changes in ploidy rates, and chromosome abnormalities might be useful in screening for hepatocarcinogens. (5 refs.)

77-0151 Cyclic Elevation of Pretumor Rat Serum Alpha-Fetoprotein During 3'-MDAB Hepatocarcinogenesis. (Eng.) Kelleher, P. C.; Nadworny, H. A.; Smith, C. J. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 691-694; 1976.

Serum α -fetoprotein (AFP) concentrations exhibited cyclic elevations during the pretumor phase of 3'-methyl-4-dimethylaminoazobenzene (MDA) hepatocarcinogenesis in 35 of 36 Fischer rats. The MDA was given as 0.06% of a riboflavin-deficient diet. The duration of the first pretumor serum AFP elevation was from 5-7 wk, beginning 3-4 wk after diet initiation; the second elevation lasted 4-6, beginning 10-11 wk after diet initiation. The max serum AFP achieved within each period of increase varied widely. The serum AFP in 15 rats showed an incomplete third pretumor elevation which was superseded by an accelerated rate of AFP production by hepatomas. (9 refs.)

77-0152 Immunochemical and Immunohistological Studies on Fetal and Other Serum Proteins in Rats During 3'-MDAB Hepatocarcinogenesis. (Eng.) Sakamoto, S.; Yachi, A.; Koike, M.; Odani, S.; Kawaharada, M.; Wada, T. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 237-245; 1976.

Changes in serum levels of albumin, seromucoid, haptoglobin, α -fetoprotein, α -acute phase protein (AAP) and other serum proteins of rats during 3'-methyl-4-dimethylaminoazobenzene (MDAB) hepatocarcinogenesis were studied. Albumin and seromucoid were detected in "oval cells" or "transitional cells" and also in some hepatoma cells. The elevation of serum AFP was demonstrated both in the stage of "oval cell" proliferation (primary response) and in the later stage of the development of cancer. The elevation of serum α -acute phase protein levels was shown prior to the "primary response"; this elevation was followed by gradual increases thereafter, until the completion of carcinogenesis. This was in agreement with the immunohistological observations. Serum AAP appeared to be a marker of cholangiocytes. (7 refs.)

77-0153 Possible Repair of Carcinogenesis by Nitroso Compounds. (Eng.) Magee, P. N.; Swann, P. F.; Mohr, U.; Resnik, G.; Green, U. In: *Fundamentals in Cancer*

Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 281-292; 1976.

The possible role of DNA repair in the organotropic actions of nitroso compounds and in defending the body against these chemicals was investigated. Experiments using N-ethylnitrosourea and N-methylnitrosourea, both of which show brain-specific carcinogenicity, indicated that repair of the corresponding O⁶-guanine lesion in the brain was very slow. The lack of organ-specific cell fractions capable of excising chemically methylated bases from DNA may be a determining factor in the selective induction of these chemicals. In other studies using dimethylnitrosamine (DMN), the potentially mutagenic O⁶-methylguanine persisted much longer in the kidney after a larger dose (20 mg/kg body wt), which induced kidney tumors, than after a smaller dose (2.5 mg/kg), which did not. To study the existence of repair processes in terms of actual tumor yield, male CFN rats were given either a single ip injection of DMN (32 mg/kg) or a single dose of 16 mg/kg followed by a second dose of 16 mg/kg. After 80 wk, tumor incidences resulting from second doses given 16 or 32 days after the first were both about 12%, much less than the number arising from a single dose (55%), indicating that repair of the initial dose had taken place. However, doses separated by 4 days or less had a cumulative effect. Thus, repair from carcinogenesis by DMN may occur. (33 refs.)

77-0154 Effects of Ethylnitrosourea Administration During Pregnancy on Three Subsequent Generations of BDVI Rats. (Eng.) Tomatis, L. (International Agency Res. Cancer, Lyons, France) Ponomarev, V.; Turusov, V. *Int J Cancer* 19(2): 240-248; 1977.

The influence of a single ip dose of 40 mg/kg of N-nitrosoethylurea (ENU) to BDVI rats on the 16th day of pregnancy was assessed. Of the 11 females given ENU, 4 either cannibalized their progeny immediately after birth or miscarried. The remaining 7 delivered a total of 63 young, 5 of which died before weaning. The body wt curves of the F₁, F₂, and F₃ generations showed a difference in wt increase between F₁ descendants from ENU-treated mothers and those from control mothers. The percentage of tumor-bearing animals was higher in ENU-treated mothers and highest in their F₁ descendants. Eight of the 11 females treated with ENU during pregnancy had tumors: 4 had tumors of the brain and 1 had a peripheral neurinoma. In the F₁ generation, nervous tissue tumors occurred in 92.5% of the females and in 82.1% of the males (total of 79 tumors in both sexes). Of these, 48 were neurinomas of the peripheral nerves, 21 were brain tumors, and 10 were spinal cord tumors. In F₂ progeny of ENU-treated mothers, no nervous tissue tumors were observed. In F₃ progeny, neurinomas were noted in one female and in two males. Prenatal exposure to a chemical carcinogen may result in an increased cancer risk. (31 refs.)

77-0155 Hematologic Effects of a Single Dose of Methyl nitrosourea. (Eng.) Seidel, H. J. (Dept Clinical Physiology, Center Basic Clinical Res., Univ. Ulm 79 Ulm/Donau, W. Germany) *Exp Hematol* 5(1): 19-26; 1977.

The hematological effects of a single dose of methyl nitrosourea (MNU; 50 mg/kg, iv) administered to CBA/5 mice were studied. Thrombocytes, lymphocytes, and granulocytes were 25%-50% of control values by day 1. Granulocytes decreased from 1,080/mm³ in controls to 330/mm³ and lymphocytes from 5,300/mm³ to 1,280/mm³. Reticulocytes were lowest on day 3. This was followed by reticulocytosis on day 7. The number of granulocytes recovered rather rapidly in the blood but remained slightly lower than control values during the observation period. Thrombocytes were depressed for the longest time, recovery starting after a delay of more than 2 wk. Blood lymphocytes appeared to have recovered on day 14 but were again low 3 wk after MNU treatment. Bone marrow cellularity decreased to approx one-third within 24 hr and remained below control values for the entire period. The initial reduction was mainly due to a disappearance of erythroblasts and a decrease of bone marrow lymphocytes. The lymphocytes were preferentially reduced 3 and 7 days after MNU treatment when the absolute number of lymphocytes was 26% and 20%, respectively, of that found in the controls. The cellularity of the spleen was approx 10%-20% higher than in controls. An increase of erythropoietic cells was seen on day 7. As early as 3 hr after MNU, pluripotent and granulocytic committed stem cells in bone marrow and spleen were reduced to 20%-50% and 10%-20%, respectively. The pluripotent cells then stayed at approx 10% until day 7 and returned to normal levels after 3 wk. The granulocytic cell values were lowest on day 3 and, in contrast to the pluripotent cell values, demonstrated a 50% recovery in the spleen and an even greater recovery in the bone marrow on day 7. The data support the contention that MNU is toxic for the hematopoietic cell renewal system. (14 refs.)

77-0156 13-cis-Retinoic Acid: Inhibition of Bladder Carcinogenesis in the Rat. (Eng.) Sporn, M. B. (NCI, Bethesda, MD 20014) Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L.; Springer, S. *Science* 195(4277): 487-489; 1977.

The inhibition of bladder cancer induced by the direct instillation of N-methyl-N-nitrosourea (NMU) into the urinary bladder of female Wistar/Lewis rats was investigated. Three doses, each 1.5 mg, were given at biweekly intervals to five groups of 23 rats each. Group A was fed a standard laboratory diet for the duration of the experiment. Groups B and C were fed 13-cis-retinoic acid, 120 and 300 mg/kg of standard diet, respectively, beginning at the time of the first NMU instillation. Groups D and E were similar to groups B and C except that the retinoid was not initiated until 1 day after the three NMU treatments had been completed. All surviving rats were killed 9 mo after the initial dose of carcinogen. It was found that 13-cis-retinoic acid inhibited the development

of the epithelium: the number of areas that had papillomas or carcinomas was diminished markedly. In groups D and E, this inhibitory effect was independent of any carcinogenic effects, since the retinoid was not started until after all free carcinogen had disappeared. In addition to the more predominant transitional cell papillomas and carcinomas, squamous cell carcinoma of bladder epithelium was also inhibited. 13-cis-Retinoic acid also diminished the presence and extent of flat, proliferative lesions, which had varying degrees of hypercellularity and atypia, and squamous metaplastic lesions. The retinoid had a highly significant ability to diminish the severity of preneoplastic lesions. (26 refs.)

77-0157 Metabolic Fate of N-n-Butyl-N-(4-hydroxybutyl)nitrosamine and Its Analogues. Selective Induction of Urinary Bladder Tumours in the Rat. (Eng.) Okada, M. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan) Ishidate, M. *Xenobiotica* 7(1/2): 11-24; 1977.

The metabolic fates of N-n-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) and N,N-di-n-butylnitrosamine (DBN) were investigated after po administration to rats and other animals. The major urinary metabolite, more than 40% of the original dose, was N-n-butyl-N-(3-carboxypropyl)nitrosamine (BCPN). The carcinogenicity of BBN, DBN and their metabolites was also studied. Selective induction of bladder cancer in rats was 100% with BBN, but DBN produced only hepatomas. BCPN po also had a 100% induction of bladder cancer, and >40% of the dose was recovered unchanged from the urine of the rats. The urinary excretion of BCPN in the guinea pig was much lower than that in the rat, but that of another metabolite, N-n-butyl-N-(carboxymethyl)nitrosamine (BCMN), was higher in the former than in the latter. Furthermore, increased urinary excretion of glucuronides was observed with BBN and DBN, with a higher glucuronylation activity occurring in the guinea pig than in the rat. A good correlation was obtained between the carcinogenicity and mutagenicity of BBN and DBN. It is suggested that there may be a correlation of metabolism and structure with the organotropic carcinogenicity of BBN analogs. (41 refs.)

77-0158 Tumorigenicity of Trinitrosotrimethylene Triamine Dissolved in Dimethyl Sulfoxide. (Ger.) Urban, H. (Pathologisches Institut, Friedrich-Schiller-Universität, DDR-69 Jena, Ziegmühlweg 1, E. Germany) *Arch Geschwulstforsch* 46(8): 657-662; 1976.

The carcinogenic effect of a dimethyl sulfoxide (DMSO) solution of trinitrosotrimethylene triamine (TTT), was studied in female Wistar rats. Applied po or ip in short-term preliminary experiments, TTT in DMSO increased mitosis in the adrenal cortex significantly. In long-term carcinogenicity tests, the animals received initially 0.8-2.1 mg/3x/wk through a gastric probe. The impaired health status warranted several pauses of up to 1 wk from the seventh week till the end of the 11th month, after which time a 90-day pause

was necessary. The treatment was then continued until day 476 at one to two doses/wk, with four 1-wk pauses. The tumor yield was 100%; five cholangiomas and one hepatoma were found in five animals autopsied on day 362, after administration of a total dose of 153 mg/animal. Four cholangiomas, five hepatomas, and two liver carcinomas were found in five animals autopsied on day 470 (total dose of 174 mg). Nine cholangiomas, nine hepatomas, and three liver carcinomas were found in nine rats killed on day 567 (total dose 174 mg). Papillary hyperplasia of the epithelium of the forestomach (2 animals), chromophobic hypophyseal adenomas, mammary fibroadenoma, paravaginal mixed tumor, and leukemia were also found; these neoplasias were probably spontaneous. According to literature data, TTT, applied po, and DMSO are not carcinogenic when given alone, which suggests the possible cocarcinogenic effect of DMSO. In another experiment, pregnant Wistar rats received a single dose of TTT (30% of LD₅₀) in DMSO po, sc, or ip during the last trimester. Their offspring developed only spontaneous tumors at the usual incidence rate. (15 refs.)

77-0159 Metabolic Degradation of Stable-Isotope-Labeled Dimethylnitrosamine by Rat Liver. (Eng.) Cottrell, R. C. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England) Lake, B. G.; Phillips, J. C.; Gangolli, S. D. *Biochem Soc Trans* 5(1): 311-312; 1977.

Stable-isotope (deuterium) derivatives of dimethylnitrosamine (DMN) were exposed to metabolism by 10,000 x g supernatant of rat liver in the presence of O₂ and NADPH. The production of labeled compounds was not consistent with the most widely accepted theory of DMN metabolism, which postulates hydroxylation of an α -carbon, followed by spontaneous breakdown to methanol, formaldehyde and N₂. (6 refs.)

77-0160 Metabolic Aspects in Organotropic Carcinogenesis by Dialkylnitrosamines. (Eng.) Okada, M. In: *Fundamentals in Cancer Prevention: Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 251-266; 1976.

The relationship between the metabolism and organotropic carcinogenicity to the urinary bladder of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) and N,N-di-n-butylnitrosamine (DBN) was investigated in rats. The principal metabolite of both BBN and DBN was identified as N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN). BCPN is a selective and potent bladder carcinogen, and is thus the ultimate active form of these compounds. Several BBN analogs having 4-hydroxybutyl, 3-hydroxypropyl, or 2-hydroxyethyl groups were investigated to determine their metabolism, carcinogenicity, and target organs in the rat. The principal urinary metabolite of these compounds was general-

ly the corresponding carboxylic acid. The 3-hydroxypropyl analogs were not carcinogenic, whereas the 2-hydroxyethyl analogs induced esophageal hepatomas and papillomas, but no bladder tumors. Evidence indicates that an essential, though not sufficient, structural requirement in N,N-dialkylnitrosamines for the selective induction of bladder cancer is a 4-hydroxybutyl chain (which is metabolized to a 3-carboxypropyl group), rather than a dibutyl structure. The diverse metabolic activation of DBN is also discussed; the ω -oxidation of DBN seems to be responsible for the specific induction of bladder cancer. Results of assays for the mutagenicity of N-alkyl-N- α -acetoxyalkyl nitrosamines may support the α -hydroxylation hypothesis concerning the metabolic activation of N,N-dialkyl nitrosamines. (35 refs.)

- 77-0161 Mechanisms of Increased Alpha-Fetoprotein Production by Hepatic Injury and Its Pathophysiological Significance.** (Eng.) Watanabe, A.; Taketa, K.; Kosaka, K.; Miyazaki, M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): 209-217; 1976.

Marked elevations of serum α -fetoprotein (AFP) concentrations occurred in rats 4 days after single administrations of various hepatotoxins. The max level of serum AFP after a single dose of carbon tetrachloride (CCl_4) was much lower than after partial hepatectomy. Mitomycin *in vivo* prevented this increase in serum AFP in CCl_4 -injured rats but not in the partially hepatectomized rats. Little elevation of serum AFP was observed with a lower dose of thioacetamide (5 vs 20 mg/100 g body wt) and was accompanied by a markedly increased incorporation of ^3H -thymidine into liver DNA without any evidence of liver injury. A single administration of ethionine, which caused extensive fat accumulation with negligible necrosis of liver cells, produced a prompt and nearly 40-fold increase in serum AFP level before a detectable increase of hepatic DNA synthesis. Injections of ATP lowered the max attainable level of serum AFP after ethionine treatment. These results suggest that the elevation of serum AFP is not primarily related to the stimulation of hepatic DNA synthesis. An AFP-specific gene activation associated with liver cell injury appears to play a major role in the increased AFP production by injured liver. (6 refs.)

- 77-0162 Ethionine-Induced Activation of Embryonic Genes.** (Eng.) Hancock, R. L.; Forrester, P. I.; Lorscheider, F. L.; Lai, P. C.; Hay, D. M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 247-251; 1976.

Rat serum α -fetoprotein (AFP) levels, measured by radioimmunoassay, can be induced after only 3 days of treatment with the hepatocarcinogen, DL-ethionine. Serum AFP levels were 12-fold the control level after 13 days of the 1%-ethionine diet. tRNA methylase activity was also increased by ethionine. Another carcinogen, dimethylaminoazobenzene, did not increase serum AFP during 36 days of ethionine

intake. This induction may be caused by derepression of an embryonic gene. (14 refs.)

- 77-0163 Histochemical and Biochemical Studies on Carcino Fetal Proteins During 3'-Methyl-4-Dimethylaminoazobenzene Hepatocarcinogenesis.** (Eng.) Onoe, T.; Kaneko, A.; Yoshida, Y.; Dempo, K.; Chisaka, N.; Yokoyama, S.; Ogawa, K. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 227-236; 1976.

α -Fetoprotein (AFP) and enzyme activities were examined in individual neoplastic nodules and in hepatomas induced by 3'-methyl-4-dimethylaminoazobenzene in male Wistar rats. Each histological type of hepatoma showed characteristic enzyme activities. In hepatoma tissues, the biochemical activity of enzymes characteristic of adult hepatocytes decreased, and isozyme patterns deviated toward those of fetal liver. In histologically uniform, undifferentiated carcinoma, the enzyme activities were somewhat different for each cell or tumor, and some cells showed isozyme patterns and ultrastructural features like those of the epithelial cells of the small intestine. The deviation in isozyme patterns toward that of fetal liver was also observed in the preneoplastic nodules. The nodules, predominantly composed of eosinophilic and hydropic cells, showed an elevated esterase activity, while the nodules composed of basophilic cells showed a lower esterase activity. AFP was almost entirely negative in these nodules, while γ -glutamyl transpeptidase activity increased markedly. These observations suggest that stepwise dedifferentiation occurs in hepatocarcinogenesis. (21 refs.)

- 77-0164 Carcinogenesis Studies with Urethane. I. The Susceptibility of CFLP/Lati and Other Mouse Strains Against Carcinogenic Action of the Substance.** (Hun.) Bojan, F. (Debreceni Orvostudományi Egyetem, Kozegeszsegtani és Jarvanytani Intezet, Debrecen, Hungary) Dauda, G. *Magy Onkol* 20(4): 232-237; 1976.

The susceptibility of CFLP/Lati mice to the carcinogenic action of urethane was investigated. The animals were highly susceptible. The number of inducible pulmonary adenomas was increased by increasing both the dose of urethane and the time between treatment and sacrifice of the mice. This strain has a high frequency of spontaneous lung adenomas. It is concluded that this strain is suitable for studies on the carcinogenesis with urethane. (12 refs.)

- 77-0165 Hydrazine Activation of Guanylate Cyclase: Potential Application to Tobacco Carcinogenesis.** (Eng.) Vesely, D. L. (Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL 33152) *Biochem Biophys Res Commun* 74(2): 780-784; 1977.

The stimulation of guanylate cyclase, which catalyzes the

production of guanosine 3',5'-monophosphate (GMP), by hydrazine was investigated in male Sprague-Dawley rat tissue. At a max concentration of 100 mM, hydrazine activated guanylate cyclase 45-fold in the liver, 39-fold in the colon, 22-fold in the stomach, 19-fold in the heart, 18-fold in the pancreas, 8-fold in the lung and kidney, and 4-fold in spleen. The increases in cyclic GMP secondary to guanylate cyclase activation were highly significant in all these tissues. Of relevance to tumor induction is the fact that cyclic GMP is involved in several processes related to cell growth and has recently been implicated in cells undergoing malignant transformation. Thus, if cyclic GMP is a significant factor in malignant transformation, the ability of hydrazine, a chemical carcinogen in tobacco and tobacco smoke, to induce tumors may be related to its capacity to activate guanylate cyclase, which would in turn increase the production of cyclic GMP. Since hydrazine (H_2H-NH_2) activates guanylate cyclase as well as or better than the nitrosamines and sodium azide (NaN_3), it appears that the N-N bond, or in some cases the N-O bond, is critical for guanylate cyclase activation and, perhaps, tumor induction. (22 refs.)

77-0166 Choroidal Melanoma: Possible Exposure to Industrial Toxins (Letter to Editor). (Eng.) Albert, D. M. (Massachusetts Eye and Ear Infirmary - Harvard Medical Sch., Boston, MA 02114) *N Engl J Med* 296(11): 634-635; 1977.

Two cases of choroidal melanoma and one of squamous-cell carcinoma of the conjuction occurred in 1971-1974 among workers in a chemical plant; this occurrence rate is sixfold the expected rate ($p = 0.023$). The chemical plant uses three chemicals classified as possible human carcinogens: dimethylsulfate, hydrazine, and 4,4'-methylene dianiline. Because of the possible role of chemicals in the etiology of choroidal melanomas, detailed occupational histories should always be obtained. (9 refs.)

77-0167 Methoxsalen and Multiple Basal Cell Carcinomas [Letter to Editor]. (Eng.) Moller, R. (Copenhagen, Denmark) *Arch Dermatol* 112(11): 1613-1614; 1976.

The case of a 41-yr-old woman who had vitiligo since approx 14 yr of age is reported. The patient participated in a double-blind study of therapy with methoxsalen and sunlight. Doses of 20-23 mg of methoxsalen per day were administered, averaging 0.5 mg/kg body wt during a period of 91 days. The tablets were taken 2 hr before exposure to light, which eventually totaled 175 hr. During treatment, moderate erythema of the skin developed at the vitiligo sites. The normal skin areas became darkly pigmented, but they were without clinical signs of pathologic changes. A yr later the patient noted for the first time numerous small, slightly pigmented, red, scaling lesions on the trunk. Because the lesions became en-

larged, the patient was reexamined. On that occasion, the patient stated that she had been given 1,000 mg of arsenic trioxide for a yr 7 yr previous. Clinical examination demonstrated multiple, pigmented, superficial basal cell carcinomas from 1 to 10 mm in diameter that were localized in normally pigmented skin of the trunk. Neither melanosis nor keratoses were observable. The largest tumors were removed by curettage. The histologic diagnosis was carcinoma basocellulare (solid dermal tumor islets composed of dense, dedifferentiated, basal-cell-type epithelial cells with a peripheral palisade arrangement). (3 refs.)

77-0168 Transplantable Lines and Cell Cultures Obtained from Intestinal Carcinomas Chemically Induced in Rats. (Fre.) Martin, M. S. (Laboratoire d'Immunologie, Faculte de Medecin e, Boulevard Jeanne-d'Arc, F 21000 Dijon, France) Martin, F.; Justrabo, E.; Turc, C.; Lagneau, A. *Biol Gastroenterol (Paris)* 9(3): 185-192; 1976.

The characteristics of cultures of transplantable lines obtained from six intestinal carcinomas chemically induced (N-methyl-N'-nitro-N-nitrosoguanidine) in syngeneic rats are discussed. Each line maintained its own biological, morphological and histochemical characteristics through serial transplantation. Four of the lines have been established as continuous cultures. After trypsinization and sc injection into the syngeneic rats, these cultures gave rise to carcinomas morphologically identical to the original graft. (20 refs.)

77-0169 Comparative Study of the Metabolism of Different Analogs and Metabolites of a Natural Hepatocarcinogen, Safrole, in Rat Liver Cell Culture. (Fre.) Janiaud, P. (Groupe de Recherche sur la Differentiation Biochimique des Cellules Eucaryotes en Culture, ERA CNRS 267, Faculte de Medecine, Dijon, France) Delaforge, M.; Levi, P.; Maume, B. F. *C R Soc Biol (Paris)* 170(5): 1035-1041; 1976.

The metabolism of the hepatocarcinogen, safrole, and its analogs isosafrole and eugenol was studied in riboflavin-free cultures of male and female rat liver epithelial cells. The metabolites of safrole were identified as 2',3'-dihydro-2',3'-dihydroxysafrole, 4-(2',3'-epoxypropyl)catechol, 3'-hydroxyisofafrole, and, with eugenol as an intermediary, 2',3'-dihydro-2', 3'-dihydroxyeugenol. Isosafrole yielded 1',2'-dihydro-1', 2'-dihydroxysafrole and 1'-hydroxysafrole. The findings indicate the existence of an epoxide diol-type metabolism of safrole, isosafrole, and eugenol and the involvement of common enzymes in the metabolism. The probability of the epoxide ring being opened by epoxide hydratase is different for the different analogs. Epoxysafrole constitutes a substrate for the enzymes that open the methylene-dioxy cycle. The epoxide hydratase inhibitor 1,2-epoxy-3,3,3-trichloropropane also inhibits the enzymes catalyzing the transfer of methylene. Methylene dioxybenzene appears to be an effective competitor of safrole in the formation of water-soluble metabolites, but 1,2-epoxy-3,3,3-trichloropropane en-

hances the formation of these metabolites. The cytotoxicity of safrole appears to be linked to the methylene-dioxy cycle. (10 refs.)

- 77-0170 Fibrosarcomas Induced by Cobalt Chloride (CoCl₂) in Rats.** (Eng.) Shabaan, A. A. (Dept. Biochemistry, Univ. Surrey, Guildford, GU2 5XH, England) Marks, V.; Lancaster, M. C.; Dufeu, G. N. *Lab Anim* 11(1): 43-46; 1977.

Cobalt chloride (CoCl₂) was administered to 20 male Wistar albino rats in doses of 0.4 mg/kg/day, sc into the central abdominal wall, over a 1-yr period. At the end of 1 yr, there were 11/20 survivors, 8 of whom developed tumors. The tumors all appeared as sc masses; histological examination revealed fibrosarcomas. Some were pleomorphic, and one had the appearance of a fibromyxosarcoma. There were ulcerations in 3/8 tumors, and sites of occurrence included: the back (3), flank (2), abdomen (2), and thorax (1). In 4/8 cases, the tumor was far from the site of injection. In addition, in the CoCl₂-treated rats hyperlipemia persisted throughout the entire 12-mo experiment. These data are discussed in relation to patients who receive CoCl₂ for the treatment of chronic renal failure. (26 refs.)

- 77-0171 Study of Hamster Embryo Cells Cultured for 1-3 Years with or Without Treatment with Chemical Carcinogens: Transplantability, Growth, and Karyotype (Meeting Abstract).** (Fre.) Papadopoulos, D. (Fondation Curie-Institut du Radium, Section de Biologie, 26 rue d'Ulm, 75231 Paris, France) Mazabraud, A.; Chamaillard, L.; Hubert-Habart, M. *J Microsc (Paris)* 27(1): 19a; 1976. (no refs.)

- 77-0172 Regulation of tRNA Methyltransferase Activity in Onco-Developmental Systems.** (Eng.) Trewyn, R. W. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 101-106; 1976.

Structural analogs of S-adenosylhomocysteine (Ado-Hcy) were studied for their ability to inhibit tRNA methyltransferases, and compounds that inhibit the degradation of Ado-Hcy hydrolase were examined. In normal rat liver and Novikoff hepatoma, S-tubercidinylhomocysteine was a better inhibitor than Ado-Hcy; the N⁶-methyladenosine analog was less effective. Since blocking the hydrolysis of Ado-Hcy is another method of raising the levels of this inhibitor, inhibitors of this enzyme were tested. Adenine arabinoside, adenosine, 2'-deoxyadenosine and inosine were the most potent inhibitors. However, many of the purines and nucleosides are normal cellular metabolic products and would be of limited use in vivo. N⁶-methyladenosine may have the most promise. Since some of the agents effective in the degradation might

be acting through their inhibition of adenosine deaminase, this possibility was examined. N⁶-methyladenosine and purine riboside fit into this category; 2'-deoxyadenosine and adenine arabinoside were substrates for adenosine deaminase. (9 refs.)

- 77-0173 Trypan Blue Identification and Teratogenic and Oncogenic Activities of its Coloured Constituents.** (Eng.) Field, F. E. (Biochemistry Res. Unit, Keele Univ., Staffordshire, ST5 5BG, England) Roberts, G.; Hallows, R. C.; Palmer, A. K.; Williams, K. E.; Lloyd, J. B. *Chem Biol Interact* 16(1): 69-88; 1977.

Three of the colored contaminants regularly present in commercial trypan blue (TB) were identified chemically and then synthesized in sufficient quantity for biological testing, along with purified and unpurified samples of TB. Unpurified TB was teratogenic in mice and oncogenic in rats; purified TB was teratogenic, but only weakly oncogenic. The following monoazo dyes, found as contaminants of TB, possessed neither activity: 4-amino-3,3'-dimethylbiphenyl, 4-amino-3,3'-dimethyl-4'-hydroxybiphenyl, and 6-tolidine, all coupled to 8-amino-1-naphthol-3,6-disulfonic acid. It is concluded that the main blue component of TB is the teratogenic agent and that some unidentified component of the purple fraction is either responsible for the oncogenicity of unpurified TB or it potentiates the action of the blue component. (36 refs.)

- 77-0174 Mutagenicity of Neutral Red.** (Eng.) Longnecker, D. S. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH 03755) Curphey, T. J.; Daniel, D. S. *Mutat Res* 48(1): 109-112; 1977.

Neutral red (as its free purified base) and an N-nitrososarcosyl derivative were assayed for mutagenicity in the Ames *Salmonella typhimurium* bacterial reversion system using test strains TA 1535, 1536, 1537, and 1538. Increased numbers of revertant colonies were observed when TA 1537 and 1538 were incubated with neutral red free base in the presence of a microsomal activation system prepared from rat liver. In another assay, TA 1537 was apparently more sensitive to neutral red mutagenesis than TA 1538. Mutagenicity for neutral red free base, neutral red itself, and for the major impurity in commercial neutral red (thought to be 2-amino-3-methyl-8-methylaminophenazine) was confirmed using TA 98 in the presence of a liver-activating mixture. These results suggest that neutral red is a frameshift mutagen. The N-nitrososarcosyl derivative was inactive as a mutagen, suggesting either (1) that the side chain may interfere with intercalation of the compound with DNA or (2) that the amino group may be blocked by the side chain in a way that prevents metabolic activation. In view of the observation that many mutagens detected by the Ames system are carcinogens, it is suggested that the carcinogenic potential of neutral red be evaluated in mammalian bioassay systems. (12 refs.)

77-0175 **Conformation of Aromatic-Substituted Dinucleoside Monophosphates: An Extension of the Base-Displacement Theory of Carcinogenesis.** (Eng.) Brown, H. S. (Dept. Chemistry, New York Univ., New York, NY 10003) Shapiro, R. *Biochemistry* 16(6): 1229-1235; 1977.

The conformations of 12 dinucleoside monophosphates containing N⁴-phenylcytidine (C-Ph) or N⁴-(β-naphthyl)cytidine (C-βN) residues were studied using circular dichroic spectroscopy and compared with those observed in dinucleoside monophosphates modified by the carcinogen N-acetoxy-2-acetylaminofluorene (AAAF). In water, the most dramatic changes, almost complete reversal of the spectra, occurred with ApC-βN and GpC-βN. Lesser changes were observed with C-βN-pA and ApC-Ph, indicating the greater effect when adenine, rather than guanine, was the neighboring base. All major differences between the modified and unmodified compounds disappeared when the spectra were run in methanol, suggesting that the changes observed resulted from conformational shifts, which involved stacking between the naphthalene ring and an adjacent purine residue. The data from ¹H nuclear magnetic resonance spectra support these results. Although the details of the conformational shifts observed are different than those in the base-displacement model of carcinogenesis, as applied to AAAF, they would be expected to produce similar biological results. The results demonstrate that base displacement or covalent intercalation effects need not be limited to a particular substitution position in a nucleic acid. (31 refs.)

77-0176 **Overlapping of Carcinogens and Mutagens.** (Eng.) Sugimura, T.; Sato, S.; Nagao, M.; Yahagi, T.; Matsushima, T.; Seino, Y.; Takeuchi, M.; Kawachi, T. In: *Fundamentals In Cancer Prevention. Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund.* Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: University Park Press): pp. 191-215; 1976.

The importance of identifying suspected carcinogens as mutagens is evident from the recent increase in the numbers of compounds identified as both carcinogenic and mutagenic. Results supporting the correlation between the carcinogenic and mutagenic effects of compounds are reviewed. A modification of Ames' method for mutagenicity is described. An activating system from the postmitochondrial fraction of rat liver + NADPH, NADH, glucose-6-phosphate and its dehydrogenase are used and mutation of *Salmonella typhimurium* TA100 and TA98 is observed. The results of this test for 240 compounds are tabulated. The mutagenicity of a food additive, AF-2, which is carcinogenic to mice was demonstrated by this mutagenic test. A derivative of this compound was found to bind to DNA. AF-2 has been used as a preservative in Japan. Confirmation of the hazardous carcinogenic effect of cigarette smoke condensate (CCC) by its strong mutagenic effect on microbes is described. The mutagenicity of CCC is 10⁴ times its mutagenicity from its benzo(a)pyrene content, suggesting the presence of other mutagens. (68 refs.)

77-0177 **The Interaction of Vinyl Chloride with Rat Hepatic Microsomal Cytochrome P-450 In Vitro.** (Eng.) Ivanetich, K. M. (Dept. Physiology Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, South Africa) Aronson, I.; Katz, I. D. *Biochem Biophys Res Commun* 74(4): 1411-1418; 1977.

The interaction of vinyl chloride (VC) in vitro with the cytochrome P-450 enzyme system of the hepatic endoplasmic reticulum of Long Evans male rats was investigated. The binding of VC to cytochrome P-450 in vitro was studied spectrally in microsomes from uninduced, 3-methylcholanthrene (3-MC)-induced, and phenobarbital (PB)-induced rats. VC bound to hepatic microsomal cytochrome P-450 in all types of microsomes, with production of a type I difference spectrum. Hanes plots of the spectral binding of VC to cytochrome P-450 were linear for all types of microsomes. VC increased CO-inhibitable NADPH consumption by hepatic microsomes from induced rats. Induction by 3-MC did not increase the apparent max velocity much above that obtained for uninduced microsomes. However, for PB-induced microsomes, max velocity was approx fivefold greater than the apparent max velocity obtained with uninduced microsomes. The effects of inhibitors on the interaction of VC with cytochrome P-450 were determined. SKF 525A fully inhibited the binding of VC to cytochrome P-450, but it did not decrease the enhancement of CO-sensitive NADPH consumption by VC. However, metyrapone did not significantly inhibit the binding of VC to cytochrome P-450 but did inhibit the enhancement of CO-sensitive NADPH consumption by VC. The influence of incubation of hepatic microsomes from induced rats with VC on microsomal enzyme levels was assessed. The levels of cytochrome P-450, cytochrome b₅, and NADPH-cytochrome c reductase were not altered after incubation of hepatic microsomes with either VC, NADPH, or NADH. Cytochrome b₅ and NADPH-cytochrome c reductase were not affected after incubation of hepatic microsomes with VC plus NADPH, but cytochrome P-450 was decreased. The VC-mediated decrease in cytochrome P-450 was slight in control (8%) and 3-MC (7%) microsomes, but was significant in PB microsomes (31%). In PB-induced microsomes, microsomal heme was decreased by approx 30% of the decrease in cytochrome P-450. Reduced glutathione and CO inhibited the VC-mediated decrease in cytochrome P-450 in PB-induced microsomes by approx 30% and 80%, respectively. NADH supported the VC-mediated decrease in cytochrome P-450 by approx 30% in comparison to NADPH. The results may provide an explanation for the observation that prior exposure of laboratory animals to VC protects them against the toxic effects of VC. (17 refs.)

77-0178 **Alteration in Macromolecular Glycosylation of Transformed Cells Mediated by Cholera Toxin and Dibutyl Adenosine 3':5'-Cyclic Monophosphate.** (Eng.) Rieber, M. (Centre Microbiology and Cell Biology, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela) *Biochem Soc Trans* 4(6): 1073-1074; 1976.

The change in macromolecular glycosylation of transformed cells mediated by cholera toxin and dibutyryl cyclic AMP was studied. The ts-NT₁-KR cell line, a cloned derivative of normal rat kidney cells transformed by the temperature-sensitive ts 339 derivative of B77 virus, was utilized. When the cells were labeled with ³H-glucosamine, a relative decrease in the glycosylation of a Pronase-sensitive component (with a molecular wt of 250,000) was observed. This decreased glycosylation was reproducibly counteracted by addition of cholera toxin (1 µg/ml) or dibutyryl cyclic AMP (0.2 mM) to the culture medium. The altered distribution of glycosylation in cells exposed to cholera toxin and dibutyryl cyclic AMP, which was less evident in cells exposed to conditions that restricted the expression of transformation, was also manifested in immune-precipitation reactions, in which cellular glycoproteins were allowed to react with antisera versus murine leukemia virus components. In such experiments, immune serum detected a differential effect of cholera toxin on glycosylation, which appeared to depend on conditions that allowed or restricted the *in vivo* expression of malignant transformation. (5 refs.)

- 77-0179 **Evaluation of Chemical Flame Retardants for Carcinogenic Potential.** (Eng.) Loewengart, G. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY 10016) *J Toxicol Environ Health* 2(3): 539-546; 1977.

Two chemical flame retardants were studied for their carcinogenic potential. Female ICR/Ha Swiss mice were vaccinated against ectromelia, and treatments were begun when they were 6-8 wk old. Tetrakis(hydroxymethyl)phosphonium chloride (THPC) and Pyroset TKP, the mixed acetate/phosphate of the same phosphonium base, were tested as whole carcinogens, initiators, and promoters in mouse-skin-application experiments. There were 20 mice to a group. Dosages were based on short-term toxicity evaluations (3-11 wk), and the highest possible doses that gave minimal cytotoxic effects were used for the chronic exposures. The dorsal skin of the mice was shaved initially and when necessary throughout the test. All compounds were applied in 0.1 ml of solvent [dimethyl sulfoxide (DMSO) or acetone] in the interscapular region. DMSO was applied with a calibrated paintbrush, and acetone was applied by micropipet. The formaldehyde content of commercial THPC was pH-dependent and ranged from 3.79% at pH 0.4 to 14.10% at pH ≥4.5. Commercial THPC contained 16.1% chloride and had a pH of 0.4. Although the substances (HCL and CH₂O) required to produce bis(chloromethyl)ether (BCME) were all present in large amounts, BCME was not detected (the method used had a sensitivity to 0.1 ppm). As a whole carcinogen, THPC demonstrated a low order of carcinogenic activity. Both THPC and Pyroset TKP showed tumor-promoting activity. The time to first tumors was short in both these experiments, and the number of animals with carcinomas was higher than in the whole-carcinogen tests. Application to mouse skin of Pyroset TKP (7 mg/0.1 ml DMSO) and THPC (2 mg/0.1

ml DMSO), 3x/wk for 400 days, gave one squamous carcinoma in the THPC group. Both THPC and Pyroset TKP were active as tumor promoters, utilizing a single application of the initiator 7,12-dimethylbenz(a)anthracene (20 µg/0.1 ml acetone). THPC was inactive as an initiating agent in two-stage mouse skin carcinogenesis (with phorbol myristate acetate as promotor). With Pyroset TKP as promotor (7 mg/0.1 ml DMSO), 7/20 mice bore papillomas (2 progressing to squamous carcinoma). With THPC as promotor (2 mg/0.1 ml DMSO, 3x/wk), 3/20 mice bore papillomas that progressed to squamous carcinoma. THPC shows weak carcinogenic and moderate tumor-promoting activity, and Pyroset TKP shows moderate promoting activity. (25 refs.)

- 77-0180 **Long-Term Administration of DDT or Phenobarbital-Na in Wistar Rats.** (Eng.) Rossi, L. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105) Ravera, M.; Repetti, G.; Santi, L. *Int J Cancer* 19(15): 179-185; 1977.

Life-span studies were conducted on outbred male and female rats who were given either 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) mixed into the diet at a dose of 500 ppm or phenobarbital-sodium (Ph-Na) dissolved in drinking water at a dose of 500 ppm. Chronic DDT administration resulted in general hyperirritability, especially in females, and some degree of body growth retardation, whereas Ph-Na-treated females showed slightly increased body wt. Nearly all Ph-Na-treated animals developed ataxia, but, as with DDT-treated rats, this behavior was regularized when the chemical was withdrawn. Liver cell tumors developed only in treated rats; however, the total incidence of other neoplasms was higher in untreated animals. Liver tumors were seen in 45% of the DDT-treated rats and 44% of the Ph-Na treated rats. DDT-treated females seemed more susceptible to liver carcinogenesis (56%) than did males (35%), while the opposite was true of the Ph-Na group (32% in females vs 59% in males). The average age at death of rats with liver tumors was similar in both groups, corresponding to 125 wk for females and 132 wk for males. The liver tumors in both groups were grossly and histologically similar. They were nodular growths that compressed the surrounding parenchyma but did not infiltrate it. No metastases were found in the lungs or in any other organ. These tumors were considered to be hepatomas. Further studies are needed to evaluate the significance of the different hepatic tumor incidence between the sexes with DDT and Ph-Na. (30 refs.)

- 77-0181 **Pesticide Induced DNA Damage and Its Repair in Cultured Human Cells.** (Eng.) Ahmed, F. E. (Dept. Biophysics, Ohio State Univ., Columbus, OH 43210) Hart, R. W.; Lewis, N. J. *Mutat Res* 42(2): 161-174; 1977.

The effects of 13 pesticides (lindane, rotenone, chlordane, heptachlor, heptachlor-epoxy, DDT, aldrin, dieldrin, carbaryl, diquat, 2,4-D fluid, dimethoate, captan, at concentrations of 1, 10, 100, and 1,000 μ M), on the induction of unscheduled DNA synthesis in simian virus 40 (SV40)-transformed human cells (VA-4) in culture, with and without metabolic activation by rat liver microsomes were studied. All of the agents except lindane, rotenone, and DDT, either directly or upon metabolic activation, induced unscheduled DNA synthesis. The DNA repair kinetics and the size of the repaired regions resulting from treatment with four agents (carbaryl, chlordane, dieldrin, and 2,4-D fluid) were studied by 313-nanometer photolysis of repaired regions containing bromodeoxyuridine. The size of the repaired regions differed among the four, but the type of repair could be classified as either the x-ray (short) or UV-ray (long) type. (63 refs.)

77-0182 **Liver Disease in Vineyard Sprayers.** (Eng.) Pimentel, J. C. (Faculdade de Medicina, Universidade de Lisboa, Instituto de Anatomia Patologica, Avenida Professor Egas Moniz, Lisbon, Portugal) Menezes, A. P. *Gastroenterology* 72(2): 275-283; 1977.

The livers of 30 vineyard sprayers who worked with copper salt fungicides for periods of 3-45 yr (mean 18) were studied. Clinical and laboratory findings were: swelling (focal and diffuse) and proliferation of Kupffer cells (30 cases); histiocytic or sarcoid-type granulomas (7); liver fibrosis of variable degree in the perisinusoidal, portal, and subcapsular areas, accompanied by atypical proliferation of the sinusoidal lining cells (8); micronodular cirrhosis (3); angiosarcoma of the liver (1); and idiopathic portal hypertension (2). Histochemical analyses revealed abundant amounts of copper within the hepatic and pulmonary lesions of these patients. These observations and inhalation experiments with guinea pigs suggest an etiological relationship between exposure to copper sulfate and the lesions described. (33 refs.)

77-0183 **The Transplacental Effect of Carcinogenic Nitroso Compounds Formed In vivo from Carbendazim in Swiss Mice.** (Hun.) Borzsonyi, M. (Országos Kozegeszsegugyi Intezet, Budapest, Hungary) Pinter, A.; Surjan, A.; Csik, M. *Magy Onkol* 20(3): 163-171; 1976.

Different groups of inbred Swiss mice were washed with the fungicide carbendazym during the first, second, or third wk of pregnancy throughout pregnancy. Sodium nitrite (0.5 g/liter) was simultaneously added to their drinking water. Controls were given carbendazym and tap water, sodium nitrite only, or tap water only. Of the offspring of the carbendazym and sodium nitrite treated mice, 33.3% of those treated during the first wk developed malignant lymphomas, as did 38.8% of those treated during the second wk, and 70% of those treated during the whole pregnancy. The tumors were manifested between the ages of 20 and 43 wk. Type C oncornavirus was found in the cytoplasm of the offspring of mice treated in the first wk and in the intracellular spaces of those treated in the third wk. No tumors were found in the offspring of animals treated with carbendazym alone. (44 refs.)

See also:

*(Rev.): 77-0001, 77-0002, 77-0003, 77-0004, 77-0005, 77-0006, 77-0007, 77-0008, 77-0009, 77-0010, 77-0011, 77-0012, 77-0013, 77-0014, 77-0015, 77-0016, 77-0017, 77-0018, 77-0019, 77-0020, 77-0021, 77-0022, 77-0023, 77-0024, 77-0025, 77-0026, 77-0027, 77-0028, 77-0029, 77-0031, 77-0032, 77-0033, 77-0034, 77-0035, 77-0036, 77-0037, 77-0038, 77-0089, 77-0097, 77-0104, 77-0113, 77-0120.
*(Phys.): 77-0189, 77-0192, 77-0193.
*(Viral): 77-0230, 77-0231, 77-0246, 77-0264.
*(Immun.): 77-0305, 77-0306, 77-0309, 77-0315, 77-0324, 77-0354.
*(Path.): 77-0427, 77-0439, 77-0442, 77-0444, 77-0450, 77-0451, 77-0452, 77-0453, 77-0468.
*(Epid.-Biom.): 77-0521, 77-0522, 77-0524, 77-0535, 77-0536, 77-0539, 77-0543, 77-0550.

PHYSICAL CARCINOGENESIS

- 77-0184 **Target Organ for a Systemic Effect of Ultraviolet Radiation.** (Eng.) Kripke, M. L. (NCI Frederick Cancer Res. Center, Frederick, MD 21701) *Photochem Photobiol* 24(6): 599-600; 1976.

C3H/HeN(MTV-) mice, a strain of specific pathogen-free mice, were used to demonstrate that the suppression of resistance to UV-induced tumor growth is mediated via the skin. Irradiation was by six Westinghouse sunlamps, 1 hr, 3× per wk. Unshaven and shaven (dorsal side) mice received 8 or 14 wk of UV radiation prior to challenge by a fibrosarcoma tumor previously induced by UV irradiation in a C3H/HeN(MTV) mouse. Tumors were transplanted on the ventral non-irradiated side. Nine of 10 untreated control mice rejected the transplanted tumors; shaved irradiated mice were highly susceptible (10 tumors/10 mice at 8 wk). A shielding effect of hair was seen after 8 wk of UV treatment; among unshaven mice, only 5/10 mice developed tumors. However, by the 14th wk, 9/10 unshaven mice had tumors. Another group of mice were subjected to enucleation; 10/10 of these blind mice developed tumors after irradiation. None of the 10 nonirradiated enucleated mice developed tumors. (1 refs.)

- 77-0185 **Etiologic Related Studies of Ultraviolet Light-Mediated Carcinogenesis.** (Eng.) Black, H. S. (Dept. Dermatology, Baylor Coll. Medicine, Houston, TX) Chan, J. T. *Oncology* 33(3): 119-122; 1976.

Etiologic related studies of UV light-mediated carcinogenesis are presented. Two groups of 50 female hairless mice (hrhr) were maintained, one on a regular balanced meal and the other on the meal supplemented with a 2% antioxidant mixture. The supplement consisted of 1.2% ascorbic acid 0.5% butylated hydroxytoluene, 0.2% dl- α -tocopherol, and 0.1% reduced glutathione. After 1 wk of feeding, both groups of animals were subjected to daily (5 days/wk) suberythemic levels of irradiation from a mercury arc lamp. Total radiance administered was 160 joules/cm² over an 18-wk period. The initial level administered was 1.13 joules/cm²/day. This was increased by 0.28 joule/cm²/day every 2 wk until a level of 1.97 joules/cm²/day was reached. The levels of cholesterol-5 α ,6 α -epoxide(CAE) in the skin of mice receiving a balanced laboratory meal and chronic UV light reached a peak at 4 wk, declined, peaked again at 14 wk, and once again declined. This cyclic pattern was also noted in animals receiving supplemental antioxidants and chronic UV light. However, the CAE level did not peak until the eighth week in those mice receiving antioxidants, and thereafter it was consistently higher than that observed in animals on the regular diet. Supplementary antioxidants inhibited the development and severity of UV light-induced tumors. Actinically induced lesions varied from premalignant actinic keratosis, papillomas, to squamous cell carcinomas. The results are inconsistent

with the thesis of direct CAE involvement in the etiology of UV light-mediated carcinogenesis. (22 refs.)

- 77-0186 **Growth Retardation in Normal and Malignant Tissues.** (Eng.) Akanuma, A. (Dept. Radiology, Faculty Medicine, Univ. Tokyo, Hongo, Tokyo 113, Japan) *Strahlentherapie* 152(6): 542-549; 1976.

Growth retardation in malignant and normal tissues was assessed in animal and clinical experiments. In the first series of experiments, using normal pig skin, three fields, 10 cm in diameter, were irradiated with 300 KVP x-rays. A surface dose of 2,300 R was delivered in a single exposure. Biopsies were taken serially, with time, from the center of the irradiated field and from nonirradiated parts. Cells in recovery proliferated exponentially at first. Then a gradual retardation of the growth rate occurred that appeared to approach an asymptote. The proliferation pattern was similar to the curve demonstrated by malignant tumors. Data were also derived from irradiated skin metastatic nodules from a breast carcinoma. The patient was treated with 250 KVP orthovoltage x-ray. Regression and regrowth of normal and cancerous tissues were similar. The larger the dose, the quicker the tumor regressed and the later it recurred. However, tumor vol was not dose-dependent and was minimum approx 3 wk after irradiation. The asymptote of the recurrent tumor was approx the same as that of the tumor before treatment, but it appeared to be dose-dependent. The skin metastases from the breast carcinoma (about 6 mo old) were still growing but were close to the asymptote size (approx 1,000 mm³). (16 refs.)

- 77-0187 **The Influence of a Chronic Environmental Stress on Radiation Carcinogenesis.** (Eng.) Baker, D. G. (Div. Oncologic Radiobiologic Res., Claire Zellerbach Saroni Tumor Inst., Mount Zion Hosp. Medical Center, San Francisco, CA 94120) *Radiat Res* 68(3): 449-458; 1976.

The effect of a chronic environmental stress on radiation carcinogenesis is evaluated. Female CFN rats were exposed to whole-body irradiation with either sham irradiation, 600 rads of 250 kilovolt x-rays, or 300 rads of fission neutrons. When rats at 25 C were placed in a 2 C environment immediately after irradiation, there was a significant early mortality. In rats that were first acclimated to cold, then irradiated and returned to the 2 C environment, there was less early mortality and a longer median survival time, compared with the non-cold-acclimated rats. The survival of the rats placed in the 2 C environment at either 6 or 16 days postirradiation was determined. Early mortality in these two groups was reduced compared to rats placed at the 2 C environment im-

mediately after irradiation. This was reflected by an increased median survival time, although the max survival time was not significantly altered as a result of the delay. At the 2 C environment, the incidence of tumors in the sham-irradiated rats was reduced to one-half of that observed in the sham-irradiated rats at a 25 C environment. The percentage of rats in all subgroups that developed tumors after irradiation was increased compared to the incidence in the sham-irradiated rats. In both alpha- and neutron-irradiated rats, exposure to a 2 C environment reduced the tumor incidence to that seen in the sham-irradiated rats at 25 C. When there was a delay of either 6 or 16 days between irradiation and exposure to the 2 C environment, the tumor incidence was reduced to a value below that observed in the sham-irradiated rats at 25 C and, for the 16-day interval, below the incidence found in the sham-irradiated rats at 2 C. In nonirradiated rats, the proportion having lens opacities in one or both eyes was not changed by exposure to the 2 C environment, but was increased when the cold-acclimated rats were returned to the 25 C environment. At the 25 C environment, irradiation increased the incidence of lens opacities. On the basis of radiation dose, neutrons were almost 7.4x as effective as x-rays. Exposure to 2 C immediately after irradiation did not reduce the incidence of lens opacities in the x-ray group, but did reduce the incidence following neutron irradiation. A delay of 6 or 16 days between x-irradiation and transfer to the 2 C environment reduced the incidence of lens opacities. A chronic environmental stress after x- or neutron radiation may inhibit malignant transformation. (22 refs.)

77-0188 **The Role of Age in the Remote Aftereffects of External β -Irradiation of Rats.** (Rus.) Moskalev, Y. I. (No affiliation given) Shelesnova, V. I. *Radiobiologiya* 16(5): 736-739; 1976.

The role of age in the remote aftereffects of external beta-irradiation in rats was studied. Total body exposure of adult (4 to 6 mo) and young (1 mo) female rats to 200 to 1,600 rads of beta rays (Sr^{90} , Y^{90}) slightly affected their av life span. Irradiated animals had increased frequencies of benign and malignant mammary tumors and skin and bone neoplasms. The young rats developed more mammary tumors. A dose of 1,600 rads caused more frequently the skin sarcomas in young rats and basal cell and squamous cell carcinomas in adults. Bone tumors were found only in adult animals exposed to 800 to 1,600 rads. (2 refs.)

77-0189 **Reparability of Damaged Bases in Rat Hepatoma Cell DNA after Exposure to Gamma Radiation and Methylnitrosourea.** (Rus.) Gaziev, A. I. (Inst. Biological Physics, Acad. Sciences, USSR, Pushchino, Moskovskaia Oblast, USSR) Kulagina, T. P.; Kuzin, A. M. *Dokl Akad Nauk SSSR* 231(3): 743-745; 1976.

Nonscheduled enzymatic DNA synthesis was studied in rat Seidel hepatoma cells. Ascitic fluid taken on day 2 after tu-

mor transplantation was irradiated (1,500 rads/min) and then treated with methylnitrosourea (MNU: $8 \times 10^{-4}M$). The rate of DNA single-strand excision and repair was reduced immediately after exposure to γ -rays and MNU; the rat hepatoma cells retained damaged DNA for 3 hr. (12 refs.)

77-0190 **Black Light Induction of Skin Tumors in Mice.** (Eng.) Zigman, S. (Dept. Surgery (Ophthalmology), Univ. Rochester Sch. Medicine and Dentistry, 601 Elmwood Ave., Rochester, NY 14642) Fowler, E.; Kraus, A. L. *J Invest Dermatol* 67(6): 723-725; 1976.

The development of skin tumors in albino inbred mice (A/J strain) exposed to 40-watt black light fluorescent lamps for 12 hr per day for up to 1 hr is evaluated. By 4 wk, the exposed skin of the tails and ears of almost all animals exposed to the black light fluorescent lamps appeared dry, red, and inflamed. By 8 wk, these areas developed scabs. During the next 50-70 wk, alternate increases and decreases in skin inflammation, ulceration, and loss of ear skin and tail segments were noted. Between 50 and 70 wk of exposure to black light, the skin of the ears and tails of almost all of the irradiated mice had developed epidermal hyperplasia, hyperkeratosis, ulceration, fibrosis, and necrosis. Following 70-90 wk of exposure to black light, many mice developed papillomas, squamous cell carcinomas, and fibrosarcomas on the dorsal regions of their tails and upper aspects of their ears. Of the 61 animals examined between 70 and 90 wk, there were 6 papillomas, 6 squamous carcinomas, and 3 fibrosarcomas. Forty mice had varying degrees of hyperplasia, and only 5 showed none of these changes. Skin samples taken from the upper back, which was covered with hair, exhibited no abnormal changes in the irradiated animals. It is concluded that black light may be a skin carcinogen for A/J mice. (9 refs.)

77-0191 **Chronic Radiodermatitis and Skin Cancer.** (Eng.) Getzrow, P. L. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumport, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 458-472; 1976.

Of 79 patients (25 women and 54 men) with chronic radiodermatitis, 28 developed malignant skin tumors after an average latent period of 25 yr. There were 24 basal cell epitheliomas, 3 squamous cell carcinomas, and 1 keratoacanthoma. Twenty-two of the malignancies appeared in areas of chronic radiodermatitis that followed irradiation of benign, nontumorous conditions and 26 were on the face. Five of the tumors occurred in patients who received radiotherapy for skin malignancies, and one in a patient treated for an internal malignancy. Eleven patients developed keratoses and 10 developed ulcers in the areas of chronic radiodermatitis. After follow-up of 22 and 23 yr, respectively, these patients were without evidence of carcinoma. Small doses of radiation given over long periods of time, such as those used for benign conditions or those involved in occupational exposures, may be

more carcinogenic than the large, single-dose radiation used to treat malignant conditions. (50 refs.)

- 77-0192 Histogenesis of Mouse Sarcomas Induced by Implantation of Polyvinyl Chloride Film in Radiation Chimeras.** (Eng.) Moizhess, T. G. (Lab. Mechanisms Carcinogenesis, Lab. Cytogenetics, Inst. Experimental Clinical Oncology, Acad. Medical Sciences USSR, Moscow, USSR) *Exp Biol Med* 81(5): 733-735; 1976.

The histogenesis of mouse sarcomas induced by implantation of polyvinyl chloride film in radiation chimeras is evaluated. To obtain radiation chimeras, female CBA mice aged 3 mo were irradiated with γ -rays in a dose of 850-950 R. Immediately after irradiation, the animals were given an ip injection of 10^7 bone marrow cells from syngeneic CBA-T6T6 mice, differing by having two small marker chromosomes in their karyotype. Thirteen mo after irradiation, one piece of polyvinyl chloride film measuring 1.5 x 2.2 cm was implanted sc into each radiation chimera in the region of the flank. Cytogenetic analysis of 13 tumors demonstrated that 11 had no T6 markers and, consequently, arose from cells of CBA mice. In one tumor (No. 86), among the 40-45 chromosomes of the tumor cell karyotype, one chromosome similar to the T6 marker was seen. In tumor No. 79, four T6 markers were found in a near-tetraploid karyotype (89 chromosomes). This tumor arose in a secondary carrier that was a (CBA x CBA-T6T6)F₁ hybrid with one T6 marker. It was considered unlikely that the tumor could have arisen from the cells of the hybrid itself, with a subsequent doubling of the number of markers, considering the comparatively short period of stay of the plastic in the hybrid. From the time of transplantation of the plastic surrounded by its capsule from the chimera to the appearance of the tumor was 6.5 mo. It was also difficult to imagine the appearance of four markers indistinguishable from T6 chromosomes as a result of chromosomal aberrations. Most probably, tumor No. 79 developed from cells of the CBA-T6T6 mouse that was the donor of bone marrow for the chimera. Morphologically, this tumor consisted of a typical spindle-cell sarcoma, indistinguishable from ordinary sarcomas induced by implantation of plastic film. Sarcomas developing in radiation chimeras as a result of sc implantation of pieces of plastic film in the late periods after irradiation arise from cells of the irradiated animal and not from bone marrow cells transplanted into it. (7 refs.)

- 77-0193 Photosensitizing Effects of 8-Methoxypsoralen on the Skin of Hairless Mice--II. Strain and Spectral Differences for Tumorigenesis.** (Eng.) Grube, D. D. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439) Ley, R. D.; Fry, R. J. *Photochem Photobiol* 25(3): 269-276; 1977.

Two strains of genetically hairless albino mice, the HRS/J/Anl and SKH:hairless-1, were given topical applications of 250 μ g 8-methoxypsoralen (8-MOP) to the dorsal skin, followed by fractionated UV irradiation 45-60 min later. The

treatment was given five times per wk for 24 wk. No strain differences in the spectral-dependent induction of cutaneous damage or estimates of the photomediated interstrand cross-linking of epidermal DNA by 8-MOP were observed. Following fractionated exposures to emissions at principally 365 nanometers (nm), squamous cell carcinomas were induced in the photosensitized skin of both murine strains. Exposures to a broader spectrum of light resulted in the earlier appearance of tumors in the photosensitized skin of the SKH:hairless-1 mice, but few or no tumors resulted in the HRS/J/Anl strain. When mice were exposed to a fluorescent sun lamp prior to each combined treatment of 8-MOP and exposure at 365 nm to determine the influence of shorter wavelengths of UV on tumor response, there was an enhanced expression of tumors in the SKH:hairless-1 mice compared to the HRS/J/Anl strain. (13 refs.)

- 77-0194 Tumours and Viruses in Mice Injected with Plutonium.** (Eng.) Loutit, J. F. (MRC Radiobiology Unit, Harwell, Didcot, Oxon, England) Lloyd, E. L. *Nature* 266(5600): 355-357; 1977.

Experiments were conducted to determine the following: (1) if plutonium-induced tumors contain viruses, (2) if sex affects the viral status or incidence of tumors, (3) if plutonium-induced tumors are similar to those induced by radium, and (4) if tumors vary with dose and time or are different in radiation chimeras. CBA/H mice and CBA T6T6/A radiation chimeras were injected ip with polymerized plutonium citrate (^{239}Pu) at concentrations of 10, 30, and 100 nanocuries (nCi). In natural mice given 100 nCi, leukemia and osteosarcomas were observed in 2/10 males and 5/10 females. After 30 nCi, osteosarcomas occurred in 4/10 males and 8/10 females. After 10 nCi, no osteosarcomas were observed in the males, but 9/10 died of other tumors; in the females, osteosarcoma was the most common tumor (6/10). Osteosarcoma is more readily induced in females because of the response of murine bone to estrogens. Miscellaneous malignancies often occurred later than the mean time for appearance of osteosarcoma. The late onset may be related to the long retention of radioactivity and immunological imbalance. None of the chimeras developed leukemia after 100 nCi. More virus particles were seen in osteosarcomas taken from 16/19 chimeras injected with 100 nCi than in other tumors. The particles appear to be identical to those observed in osteosarcomas from CBA/H mice injected with ^{226}Ra . Further studies with larger groups of animals and smaller doses of plutonium are recommended. (23 refs.)

- 77-0195 Vasoformative Non-Osteogenic (Angio) Sarcomas of Bone-Marrow Stroma due to Strontium-90.** (Eng.) Loutit, J. F. (Medical Res. Council, Radiobiology Unit, Harwell, England) *Int J Radiat Biol* 30(4): 359-383; 1976.

The vasoformative non-osteogenic sarcomas of bone marrow

stroma due to strontium-90 are investigated. CBA/H and C3H/H mice were injected ip with Sr90Cl₂ (7-20 μ C). The vasoformative non-osteogenic tumors presented a consistent picture. The salient features were hemorrhage and blood-filled spaces. Necrosis was commonplace. Variation consisted largely in the amount of viable tumor tissue, from minimal shreds and small peripheral islands infiltrating muscle and connective tissue to significant masses of tumorous tissue. In some, the masses were associated with abundant fibrous vascular stroma. The tumor cells were strongly basophilic with multiformity of size and shape from rounded and ovoid to fusiform. Giant cells were common and were usually bizarre and uninucleate. In some cases, associated with necrosis of bone marrow or erosion of bone or spontaneous fracture, small amounts of new bone were observed in association with existing living or dead bone. Blood spaces were surrounded by a palisade of atypical cells tailing off into a surrounding net of atypical reticular cells. The commonest tumor in male mice was non-osteogenic sarcoma, while osteosarcoma was noted most often in females. Osteosarcomas were observed in CBA mice (both sexes) converted to radiation chimeras. Non-osteogenic sarcoma was found in CBA mice x-irradiated in the cephalic half when only half of the body was x-irradiated (1,000 rads) and the mice were administered Sr90. The evidence favors the bone marrow stroma as the site of origin of non-osteogenic, vasoformative tumors. Pleomorphic cells suggestive of malignancy appear, particularly in association with the dilated sinuses, as a palisade and sometimes as aggregates in the hyperplasia connective tissue. (19 refs.)

77-0196 **Thyroid Disease Following Irradiation for Benign Conditions.** (Eng.) Swelstad, J. (Dept. Surgery, Evanston Hosp., 2650 Ridge Ave., Evanston, IL 60201) Scanlon, E. F.; Murphy, E. D.; Garces, R.; Khandekar, J. D. *Arch Surg* 112(4): 380-383; 1977.

Thyroid disease in patients who were treated by radiotherapy for benign conditions of the head and neck was reported. Of the 125 patients who underwent thyroidectomies between 1967 to 1975, 106 were asymptomatic. Surgical referral was advised due to abnormal palpation with or without isotope scan. Total thyroidectomy is recommended provided it could be accomplished without undue risk to the parathyroid glands. Thirty-four percent of the resected thyroids contained carcinoma, and 20% of these had regional nodal metastasis. Palpation was found to be a more accurate method of finding carcinoma in a diseased gland than thyroid isotope scan; 88% of the carcinomatous lobes were abnormal to palpation, while only 60% of the same lobes were abnormal on isotope scan. A discussion, presenting both concurring and dissenting opinions, followed the report. (3 refs.)

77-0197 **Recovery Response of Dividing Cells in the Thymus of Whole-Body Gamma-Irradiated Mice.** (Eng.) Suci, D. (Oncological Inst., 3400 Cluj-Napoca, Romania) Uray, Z.; Maniu, M. *Int J Radiat Biol* 30(5): 409-417; 1976.

The recovery response of dividing cells in the thymus of whole-body γ -irradiated (⁶⁰Co, 100 rads/min) NMRI mice is assessed. The incorporation of ³H-thymidine into thymus and spleen was almost complete within 2 hr after injection, while the specific activity of ³²P-DNA increased up to 2 days after administration of the label. Mice were whole-body irradiated 30 min after the administration of ³²P-orthophosphate. The total activity of DNA was determined in thymus and spleen 72 hr after irradiation. The dose-response curves had a shoulder in the low dose-range. A fraction of the thymus and spleen population was represented by cells with an increased radioresistance in the high dose range. In the low dose-range, the dose-response curves had D₀ = 95 rads for the spleen and D₀ = 55 rads for the thymus. The depletion of ³²P-DNA in thymus and spleen at 24 hr after administration of hydroxyurea was determined. The pulse labeling experiment suggested a G₁ (pre-synthesis) block induced by hydroxyurea (80 mg/kg), as indicated by the decrease of DNA synthesis a few hours after administration of the drug. Mice were given 80 mg/kg hydroxyurea 30 min after the administration of ³²P-orthophosphate. At different time intervals, the animals were irradiated with 80 rads. The total activity of DNA was determined in thymus and spleen at 74 hr synchronization. If irradiation was carried out at 5 hr after administration of hydroxyurea, the radioactivity of thymus DNA was significantly increased compared with the value determined for the animals irradiated 6 hr after synchronization. The recovery max corresponded to the max of DNA synthesis. The recovery effect was absent in the spleen. Accordingly, DNA synthesis was decreased for a relatively long period after the administration of hydroxyurea. Furthermore, the animals received ³²P-orthophosphate 30 min before administration of hydroxyurea. Irradiation was carried out at 1 hr, 5 hr and 6 hr after partial synchronization. The total activity of thymus DNA was determined 72 hr after the administration of hydroxyurea. The time of irradiation corresponded to the G₁ (1 hr), synthetic (5 hr) and post-synthetic and mitotic phases (6 hr) of the cycle. No recovery occurred for the G₁ cell population. The thymic and splenic dividing cells are capable of recovery from radiation injury. (31 refs.)

77-0198 **Morphologic Changes in the Thyroid Following Low-Dose Childhood Radiation.** (Eng.) Komorowski, R. A. (Dept. Pathology, Medical Coll. Wisconsin, 8700 West Wisconsin Ave., Milwaukee, WI 53226) *Arch Pathol Lab Med* 101(1): 36-39; 1977.

The morphologic alterations in the thyroid after low-dose head and neck childhood radiation were assessed in 18 patients (9 men, 9 women) aged 21-36 yr. Twelve of the 18 patients had histologically proved thyroid malignancies: 7 men and 5 women. The primary tumor was located in the right lobe in five cases, in the left lobe in four cases, and was bilateral in three. None of the 12 patients demonstrated pulmonary, osseous, or other distant metastases. Nodes were examined in only 6/12 malignant lesions. There were three patients with ipsilateral node metastases with respect to the primary tumor, two with contralateral node involvement,

and four lesions in the isthmus. Of these, one had a bilateral distribution; all the others involved only one lobe and/or the isthmus region. The glands of all patients demonstrated significant morphologic changes in addition to the high incidence of malignancy. Multiple nodules of varying types, interstitial fibrosis, and marked variation in follicular size (especially in malignant glands) were observed. The presence of dystrophic interstitial calcifications was unique to the malignancies, and it was observed in six cases. Psammoma bodies were noted in all cases of papillary carcinoma. Two benign cases had multiple foci of lymphoid aggregations, some forming true germinal centers with patchy squamous metaplasia. Microscopic examination showed an almost two-fold higher incidence of nodules in patients having a malignancy. The two follicular carcinomas were both 0.3 cm in diameter, the nine papillary lesions ranged from 0.1 to 1.0 cm in diameter, and the one medullary lesion was 1.3 cm in diameter. There is little doubt that low-dose and cervical radiation in childhood is associated with an increased incidence of thyroid cancer. (8 refs.)

77-0199 **Irradiation of the Thyroid as a Cause of Parathyroid Adenoma (Letter to Editor).** (Eng.)

Triggs, S. M. (Dept. Pathology, Welsh Natl. Sch. Medicine, Cardiff CFA 4XN, Wales) *Lancet* 1(8011): 593-594; 1977.

Small parathyroid adenomas were observed in 28/46 adult rats that had received 5 or 10 μ Ci of ^{131}I in the first 2 days of life. No tumors were seen in nonirradiated animals. Some of the larger tumors were associated with hypercalcemia. These data suggest that parathyroid tumors can be induced by irradiation and that thyroid radiation with ^{131}I may give a tumorigenic dose to the parathyroid. (4 refs.)

See also:

*(Rev.): 77-0018, 77-0039, 77-0040, 77-0041, 77-0042, 77-0044, 77-0085, 77-0089, 77-0097, 77-0113, 77-0118.

*(Chem.): 77-0167.

*(Viral): 77-0280.

*(Immun.): 77-0374.

*(Path.): 77-0490, 77-0509.

*(Epid.-Biom.): 77-0529, 77-0545, 77-0552.

VIRAL CARCINOGENESIS

77-0200 Immunological Distinction Between Ribonuclease H Activity α and $\alpha\beta$ Forms of Avian Myeloblastosis Virus (AMV) DNA Polymerase. (Eng.) Papas, T. S. (Lab. Tumor Virus Genetics, NCI, NIH, Bethesda, MD 20014) Renzi, G. R.; Martin, W. J. *Virology* 76(2): 882-885; 1977.

The effects of antibodies raised in rabbits by administration of either of the purified forms of the reverse transcriptase of avian myeloblastosis virus (AMV), α or $\alpha\beta$, on the DNA polymerase and RNase H activities of both α and $\alpha\beta$, but the RNase H activity of each form was only inhibited by the antisera specific to that form. Antibody specifically inhibitory to the RNase H activity of $\alpha\beta$ could be absorbed by α , and antibody inhibitory to the RNase H of α could be absorbed by $\alpha\beta$. It is suggested that both antisera contain antibodies elicited by identical antigenic determinants on the common α polypeptide chain in both the α and $\alpha\beta$ forms, but that different determinants are present at the RNase H active site. The results are consistent with possible functional differences between the RNase H activity of the α and $\alpha\beta$ forms of AMV reverse transcriptase. (11 refs.)

77-0201 Chemical Modification of DNA Polymerase Phosphoprotein from Avian Myeloblastosis Virus. (Eng.) Tsiapalis, C. M. (Meloy Labs. Inc., 6715 Electronic Drive, Springfield, VA 22151) *Nature* 266(5597): 27-31; 1977.

A small, nondialyzable, acidic phosphoprotein, designated ϕ was separated from the RNA-dependent DNA polymerase (RDDP) of purified avian myeloblastosis virus (AMV) by three methods: (1) molecular sieving on Sephadex G-200; (2) isoelectric focusing on polyacrylamide gels; (3) electrophoresis using sodium dodecyl sulfate-polyacrylamide gels. The addition of phosphorylated ϕ stimulated the activity of purified AMV-RDDP with poly(C)n.dG12-18 as template by up to 10 times; however, very large quantities of phosphorylated ϕ inhibited the enzyme. Dephosphorylation of ϕ removed the stimulatory potential. A model is presented that predicts that AMV-RDDP may exist in four molecular forms at some time in the life cycle of the virion and/or during purification of the polymerase. In two of these forms, phosphorylated ϕ is present, either covalently bound to RDDP (in form I) or after proteolytic cleavage (in form IV): this helps to maintain template structure in the replicative form and permits high-fidelity copying of the template. (38 refs.)

77-0202 Target Cells for Transformation with Avian Leukosis Viruses. (Eng.) Graf, T.; Royer-Pokora, B.; Beug, H. In: *Modern Trends in Human Leukemia*

II. Biological, Immunological, Therapeutical and Virological Aspects. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 169-176; 1976.

Experiments involving a newly developed in vitro transformation assay with avian erythroblastosis virus (AEV) are reported. The infection of freshly prepared chicken bone marrow cell cultures with AEV resulted in the appearance of foci of small, refractile, round, rapidly growing cells. The staining properties of the in vitro transformed cells were indistinguishable from leukemic erythroblasts induced in vivo and maintained. The in vitro transformed cells were capable of dividing for an av of 18 to 29 generations; these values are comparable to those observed for normal or sarcoma virus-transformed chicken fibroblasts. The bone marrow cells transformed in vitro by AEV were negative for various properties characteristic of granulopoietic (myeloid) cells (they were not adherent, did not phagocytize bacteria, and were not dependent on colony stimulating factor for colony formation in semisolid agar) while bone marrow cells transformed by myeloid leukemia virus (MC29) were positive. Data on the incidence of bone marrow cells transformed by avian erythroid and myeloid leukemia viruses suggests that the target cells for leukemogenesis with chicken erythroid and myeloid leukemia viruses are not pluripotent stem cells but are committed to differentiate along the erythropoietic and granulopoietic series, respectively. (19 refs.)

77-0203 A Partial Genetic Map of Rous Sarcoma Virus RNA: Location of Polymerase, Envelope and Transformation Markers. (Eng.) Joho, R. H.; Stoll, E.; Friis, R. R.; Billeter, M. A.; Weismann, C. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology.* Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 127-145; 1976.

Maps of large T1 oligonucleotides have been determined for the Prague strain of Rous sarcoma virus, subgroup B (Pr RSV-B); avian sarcoma virus (Bratislava) B77, subgroup C; and Rous-associated virus type 6 (RAV-6); and inferred for Pr RSV-A, Pr RSV-C, and RAV-1. The RNA recombinants selected from crosses between strains differing in their biological properties and their oligonucleotide maps were analyzed and found to contain at least one, but usually multiple, crossovers. The origins of the RNA segments constituting the genome were identified and correlated with the biological properties of the recombinant. From a cross between Pr RSV-B and RAV-1, the *trf* marker (transforming capacity) was located in a region close to the 3' terminus and the *env* marker (determinant of host range) was located in the middle section of the genome. The polymerase gene (*pol*) was previously assigned to the 5'-terminal third of the genome. The partial genetic map of RSV is: (5')-*pol-env-trf*(3'). (17 refs.)

- 77-0204 Structure of Rous Sarcoma Virus RNA: 1) Localization of N⁶-Methyladenosine; 2) The Sequence of 23 Nucleotides Following the 5' Capped Terminus m⁷GpppGmp.** (Eng.) Beemon, K. L.; Keith, J. M. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 97-105; 1976.

The 10,000-nucleotide RNA genome of Rous sarcoma virus (RSV) was found to contain approx 12 N⁶-methyladenosine (m⁶A) residues. Localization of these residues relative to the 3' poly(A) end of the viral 30S-40S RNA showed that most of the m⁶A was distributed throughout the 3' third of the RNA, where the *src* gene has been mapped. At the 5' end, RSV RNA has methylated nucleosides in the m⁷GpppGmpCp capping structure. This cap has been detected as part of a large RNase T₁-resistant oligonucleotide sequence. A possible sequence has been established for the first 25 nucleotides at the 5' end of Prague B RSV 30S-40S RNA. (19 refs.)

- 77-0205 Expression of Virus Specific Morphological Cell Transformation Induced in Enucleated Cells.** (Eng.) Beug, H. (Max-Planck-Institut für Virusforschung, Biologisch-Medizinische Abteilung, Spemannstr. 35/III, D-7400 Tübingen, W. Germany) Peters, J. H.; Graf, T. *Z Naturforsch* 31(11/12): 766-768; 1976.

The role of nuclear components in the functioning of the transformation-inducing viral gene product, as judged by changes in cell morphology, was investigated using chick embryo fibroblasts. The fibroblasts, infected by a temperature-sensitive mutant of Rous sarcoma virus, were enucleated with Cytochalasin B. The cytoplasts were still able to transform morphologically when shifted from nonpermissive to permissive temperatures and to revert to their normal morphology when shifted from permissive to nonpermissive temperatures. These results suggest that the primary target for the transforming gene product does not reside in the nucleus but in the cytoplasm or in the membrane. Since the morphology of a cell appears to be largely determined by the organization of its cytoskeleton, this could be the possible target. It remains to be shown, however, that alterations of the microfilament-microtubuli system take place in enucleated fibroblasts shifted from one temperature to another. (5 refs.)

- 77-0206 Transformation of Chinese Hamster Embryo Cells with an Avian Sarcoma Virus ts Mutant.** (Eng.) Lacinova, J. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Praha 6, Czechoslovakia) *Folia Biol (Praha)* 22(5): 289-297; 1976.

The transformation of Chinese hamster embryo cells with a temperature-sensitive mutant of the Schmidt-Ruppin strain of Rous sarcoma virus subgroup A (RTSCH-68) was evaluat-

ed. A mixed culture of Chinese hamster and chicken ts 68 transformed cells was maintained at 35 C and passaged at a ratio of 1:5 twice weekly. After 5-6 wk, round, refractile cells forming small clusters could be recognized in some cultures. With further passages, the number of morphologically changed cells increased. After 24 hr at 40 C, the number of transformed cells decreased, and after 72 hr, the culture reverted to a morphology resembling uninfected cells. Analysis of the growth properties of RTSCH-68 cells revealed that the generation time of 37 hr could be found at both 35 and 40 C. The generation time of uninfected Chinese hamster cells was 38 hr and that of the transformed virogenic RSCH cells was 16.5 hr at 35 C. At the permissive temperature (35 C), avian group-specific (gs) antigen synthesis could be induced by 5-iododeoxyuridine (40 µg/ml for 48 hr). The same result was obtained by treatment of RTSCH-68 at a permissive temperature with 5-bromodeoxyuridine (100 µg/ml for 48 hr). Virus production was not activated in gs positive or gs negative RTSCH-68 cells. Lysis of casein could be found in all cases when RSCH cells were used. At the permissive temperature, RTSCH-68 cells showed complete or partial lysis in almost all cases. A 2.23-fold higher rate of glucose uptake was observed with RSCH cells grown at 35 C than with control cells grown at the same temperature. The higher values of sugar uptake at a permissive temperature were also observed for RTSCH-68 cells than for Chinese hamster embryo fibroblasts (1.65-fold higher), whereas the RTSCH-68 cells grown at 40 C revealed the same value as control embryo fibroblasts grown at 35 C. The results show that a mammalian cell line transformed by a temperature-sensitive mutant of Rous sarcoma virus has been developed. (24 refs.)

- 77-0207 Ultrastructural Study of Cell Colonies Transformed by Oncogenic Viruses (Meeting Abstract).** (Fre.) Ricciardi-Castagnoli, P. (Centro per lo Studio della farmacologia delle infrastrutture cellulari del C.N.R., Milan, Italy) Barlati, P.; Brega, A.; De Giuli, C. *J Microsc (Paris)* 27(1): 21a; 1976. (no refs.)

- 77-0208 Pseudotypes of Avian Sarcoma Viruses with the Envelope Properties of Vesicular Stomatitis Virus.** (Eng.) Weiss, R. A. (Imperial Cancer Res. Fund Labs., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England) Boettiger, D.; Murphy, H. M. *Virology* 76(2): 808-825; 1977.

A study is presented of the antigenic specificity and host range of the two pseudotypes that resulted from the superinfection of cells producing Rous sarcoma virus (RSV) with temperature-sensitive mutants of vesicular stomatitis virus (VSV). VSV genomes within particles bearing the envelope antigens of RSV were denoted VSV(RSV); RSV genomes within particles bearing the envelope antigens of VSV were denoted RSV(VSV). VSV(RSV) pseudotypes possessed the host range restrictions of RSV and were neutralized by anti-

sera to the RSV subgroup. Both pseudotypes were produced concomitantly with VSV synthesis. VSV(RSV) particles comprised up to 12% of the VSV progeny titer and RSV(VSV) up to 1% of the RSV titer. Little or no pseudotype fraction was detectable when RSV and VSV were mixed together in vitro before assay. The proportion of pseudotypes in harvests of mixed infections was not significantly reduced by removal of large virus aggregates by filtration or sonication. It is thus possible to view pseudotype formation as the assembly of RSV subgroup-specific antigens (probably gp85) into the envelope of VSV virions and of VSV antigens (probably G protein) into the envelope of RSV virions. (44 refs.)

77-0209 Infection of Human Embryo Cells with Avian Sarcoma Virus B77 In Vitro. (Eng.) Reinerova-Hladka, M. (Res. Cancer Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) *Neoplasma* 23(6): 595-599; 1976.

The infection of human embryo cells with avian sarcoma virus B77 is reported. Cells in the third passage were treated with 5-iododeoxyuridine (8 $\mu\text{g}/\text{ml}$) for 24 hr and then irradiated with visible light. The culture medium was changed for a medium containing 300 $\mu\text{g}/\text{ml}$ DEAE-dextran; 30 min later, the embryo cells were infected by B77 virus (multiplicity of infection, 5 chicken focus-forming units per cell). The infected cells were subcultured. The first signs of variation in cell morphology and growth were noted in the third passage, 30 days after cell infection. The presence of the virus genome in infected cells was tested by cell fusion with C/O chicken embryo cells in subsequent passages. The virus genome was detected in the 3rd to the 14th passages using 1×10^6 cells for fusion rescue. To determine the number of cells needed for the induction of one focus of converted chicken cells, the infected Hu(B77) cells in different passages were seeded on C/O chicken embryo cells treated with inactivated Sendai virus. The number of infectious centers was counted 8 days after the fusion. The number of cells needed for positive rescue increased with increasing passages of Hu(B77) cells. To determine whether the Hu(B77) cells were producing infectious virus into tissue culture medium, the fluid was filtered through a Millipore filter, concentrated 100 times by ultracentrifugation, and the virus preparation was inoculated into 1-day-old chickens. Small virus production was observed in subsequent passages starting from the eighth passage. Virus production was also found in cells adapted to 5-bromodeoxyuridine. The virus genome was detected in 9/11 clones tested. The Hu(B77) cells did not have the transformed phenotype. The growth properties of infected Hu(B77) cells, cells of Hu(B77) clone IC, and control cells were similar. It is not known whether the observed differences can be connected with a different mode of persistence of the virus genome in the cell or with a different expression of viral genes. (14 refs.)

77-0210 An In Vitro Study of the Oncogenic Effects of Two Variants of Avian Sarcoma Virus B77 on Rat Embryonal Fibroblasts. (Eng.) Hlubinova, K. (Cancer

Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) Simkovic, D.; Valentova, N.; Chalupa, I.; Matoska, J. *Neoplasma* 23(6): 601-608; 1976.

The oncogenic effects of two variants of avian sarcoma virus B77 on rat embryonal fibroblasts (LWF) were investigated. LWF cultures were infected with 22-B77V as follows: the medium was removed from the grown cell culture, containing approx 2×10^6 cells, and 1 ml of concentrated virus (titer 1.6×10^6 focus-forming units/ml) was added. The infected culture was kept for 60 min, and then the medium was added. At 7 and 15 days, subcultivation was carried out, and the virus was added to the cells. The infected cells were then maintained through subcultivation for 37 passages. No permanent changes were observed during in vitro subcultivation. All tests for the presence of infectious virus proved to be negative, as did transplantation tests for tumorigenous cell activity. LWF cells present in 13th passage in vitro were infected with 55-B77V in a similar manner with a concentrated viral preparation (5.2×10^5 units/ml). At 38 days after first addition of the virus, foci of morphologically different spherical cells with a granulated cytoplasm appeared. This type of cell rapidly outgrew the others, and after two to three subcultures, only this type of cell was present. The cells grew in clusters, frequently three-dimensional. Their growth rate as well as acidification of the medium was more rapid. Morphologically altered cells continuously released biologically active virus into the culture medium as of the 20th passage. Virus-transformed cells (LWFB55) have survived for more than 3 yr, and they persist permanently altered morphologically. Karyological analyses of transformed LWFB55 cells were made during the 55th-60th passages. The number of chromosomes was 56-115. There were three types of marker chromosomes: large metacentric chromosomes with index 1.1-1.5, submetacentric chromosomes with index 2.1-2.2, and microchromosomes. Marker chromosomes were present not only in mitotic figures containing modal numbers of chromosomes but also in those with either a larger or a smaller number. (15 refs.)

77-0211 Synthesis of Viral RNA in Cells Infected By Avian Sarcoma Viruses. (Eng.) Bishop, J. M.; Deng, C. T.; Mahy, B. W.; Auintrell, N.; Stavnezer, E.; Varmus, H. E. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press): Vol. 4, pp. 1-20; 1976.

Cells infected with avian sarcoma virus (ASV) synthesize viral RNA by transcribing an integrated DNA provirus. The production of viral messengers was interrupted by the antibiotic cordycepin without major effect on primary transcription. Duck cells producing virus contained at least two separate classes of viral messenger RNA (molecular wt 3×10^6 and 1.3×10^6) that could permit independent expression of different viral genes. In mammalian cells transformed by ASV only the smaller class of viral messenger (1.3×10^6) was detectable in cytoplasm. ASV-infected hamster cells that had

reverted to a normal phenotype retained provirus and produced messenger for the viral transforming gene. The amount of this message was smaller than in the parental transformed cells. The revertant phenotype was attributed to a reduction in dose for the product of the viral transforming gene. (23 refs.)

- 77-0212 **Transcription of Avian Sarcoma Virus RNA.** (Eng.) Taylor, J. M.; Illmensee, R.; Trusal, L. R.; Summers, J. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, G. A.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 161-173; 1976.

Studies on the initiation and subsequent elongation of the DNA transcripts of avian sarcoma virus RNA made in vitro by the viral polymerase are reported. The mechanism by which transcripts > 100 nucleotides are made is discussed in terms of a model of genome circularization and in terms of studies involving digestion of the DNA product with restriction enzymes. When the endogenous reaction of detergent-disrupted virions is restricted by the availability of nucleoside triphosphates, the majority of the DNA transcripts obtained are initiated on the transfer RNA (tRNA) primer and are not longer than about 100 nucleotides. The studies indicate that the 110-nucleotide DNA species is transcribed from near the 5' terminus of the genome. When DNA synthesis is not restricted, DNA transcripts initiated on the tRNA primer can be elongated to > 2,500 nucleotides. For such elongation to occur, it is believed that the 5'-terminal region of the genome juxtaposes with a 3'-terminal region of either the same or another 35S RNA. The former event is equivalent to the formation of a circle. Further studies indicate that the majority of large tRNA-primed DNA transcripts begin with a similar sequence of at least 160 nucleotides. Since only 110 nucleotides can be transcribed from the 5' terminus of the genome, the remaining 50 nucleotides must have been transcribed from a separate unique location on the genome. (13 refs.)

- 77-0213 **Characteristics of Virus-Specific RNA in Avian Sarcoma Virus-Transformed BHK-21 Cells and Revertants.** (Eng.) Deng, C. T. (Dept. Microbiology, State Univ. New York at Stony Brook, Stony Brook, NY 11794) Stehelin, D.; Bishop, J. M.; Varmus, H. E. *Virology* 76(1): 313-330; 1977.

Several characteristics of avian sarcoma virus (ASV) RNA transcripts were compared in transformed and reverted clones of baby hamster kidney (BHK) cells using hybridization with highly labeled, single-stranded, complement DNA (cDNA) synthesized by the DNA polymerase of ASV (ASV cDNA) to detect virus-specific RNA. Viral transcripts in both transformed and reverted clones contained poly(A) sequences and were associated with polyribosomes. In both clones viral RNA was three times more abundant in the cytoplasm than in the nuclei. In the transformed clone, whole-cell RNA contained 35S and 24S ASV RNA, but only 24S ASV

RNA was detected in the cytoplasm; in the reverted clones, 24S ASV RNA was present in whole-cell RNA and in poly-(A)-containing cytoplasmic RNA, but the amounts of viral RNA were too low to determine whether they also contained 35S ASV RNA. By using a hybridization reagent specific for nucleotide sequences required for transformation by ASV (cDNAsarc), it was shown that polyribosomal RNA in both transformed and reverted cells contains transformation-specific sequences. The concentration of these sequences, however, reflects the overall concentration of viral RNA in the cells. Therefore, no qualitative difference could be found in the pattern of viral gene expression in these phenotypically varied cells. A reduction in the concentration of viral RNA may be the only change in viral gene expression in the reverted cells. (55 refs.)

- 77-0214 **Studies with DNA Complementary to the Glycoprotein Gene(s) and to the 3'-End of the Avian Sarcoma Virus Genome (Meeting Abstract).** (Eng.) Tal, J. (Dept. Microbiology, Univ. California, San Francisco, CA) Fujita, D.; Varmus, H. E.; Bishop, J. M. *Isr J Med Sci* 12(11): 1390; 1976. (no refs.)

- 77-0215 **Expression of Viral Proteins in Mammalian Cells Transformed by Avian Sarcoma Viruses.** (Eng.) Aupoix, M. (Unite de Virologie Fondamentale et Appliquee, INSERM, 69008 Lyons, France) *Int J Cancer* 18(6): 787-797; 1976.

The expression of viral proteins in rat and hamster cells transformed by avian sarcoma viruses (ASV) was evaluated by indirect immunofluorescence. When the cytoplasmic expression of p proteins was studied with the polyvalent anti-group-specific serum, significant differences were observed between the lines, but no correlation was noted among the degree of fluorescence of the cells, their capacity to stain with higher serum dilutions, or the class to which they belonged. The four cell lines in which the highest degree of expression of group-specific antigen(s) was observed belonged to virus-producer (RBHtc), inducible nonproducer (RS2/3), inducible but helper-dependent nonproducer (RB12/5), and noninducible nonproducer (TWERC) cells. A relatively low degree of expression of the group-specific antigens was also noted in the second virus-producer line 17RBI77. Study of the cytoplasmic expression of p27 with the monospecific antiserum showed that this expression did not appear to parallel the overall expression of the group-specific antigens. The highest degree of expression of gp85 and of the p proteins detected by the anti-group-specific serum was found on the two virus-producer lines, RBHtc and 17RBI77, and the two most inducible nonproducer subclones, RS2/3 and RS2/10. The p27 did not appear to be inserted in the membrane of any cell line, but gp85 and some p proteins other than p27 became inserted coordinately in the membrane of the virus-producer and the most inducible nonproducer cells. Viral proteins were either not inserted or inserted in undetectable amounts in the membrane of the least-inducible nonproducer cells. There may

exist translational and/or posttranslational controls of the expression of viral proteins in the ASV-transformed mammalian cells. (42 refs.)

- 77-0216 **Transcription of the Avian RNA Tumor Virus Glycoprotein Gene in Uninfected and Infected Cells.** (Eng.) Hayward, W. S.; Wang, S. Y.; Urm, E.; Hanafusa, H. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press): vol 4, pp. 21-35; 1976.

Bryan Rous sarcoma virus (BH-RSV) is a defective virus that appear to have a deletion of at least part of the gene that codes for the envelope glycoprotein. Schmidt-Ruppin RSV-N8 virus (SR-RSV-N8), also deleted in the glycoprotein gene, has been isolated from wild type SR-RSV and has properties similar to those of BH-RSV. Certain cells, termed chicken helper factor positive (chf+), can complement the defective virus, supplying an envelope glycoprotein that confers subgroup E specificity. Virus-specific RNA is present in uninfected chf+ cells, but barely detectable in chf- cells. Using selective hybridization techniques, RAV-2 ³H-labeled complementary DNA (cDNA) sequences corresponding to the deleted region of BH-RSV were isolated. This cDNA hybridizes extensively (71%-96%) to RNA from infectious viruses, including RAV-0, RAV-2, RAV-7, and wild type SR-RSV, but does not hybridize with RNA from BH-RSV (<2%) or SR-RSV-N8 (<4%). Thus the selected DNA (cDNA_{env}) appears to be specific for the envelope glycoprotein gene (env). The cDNA_{env} was used to analyze the expression of the env gene in both uninfected and infected cells. Little or no env RNA was detectable in uninfected chf- cells, but significant amounts of this RNA were present in the chf+ cells. Infection of these cells with BH-RSV did not alter the level of the endogenous glycoprotein RNA, although the exogenous BH-RSV specific RNA was synthesized at very high levels. Thus the exogenous and endogenous virus genomes within the same cell appear to be regulated independently. (33 refs.)

- 77-0217 **Phenotypic Mixing Between Avian and Mammalian RNA Tumor Viruses: I. Envelope Pseudotypes of Rous Sarcoma Virus.** (Eng.) Weiss, R. A. (Imperial Cancer Res. Fund Labs., P.O. Box 123, Lincoln's Inn Fields, London, WC2A 3PX, England) Wong, A. L. *Virology* 76(2): 826-834; 1977.

Studies are presented that indicate that phenotypic mixing between envelope antigens of avian and mammalian C-type viruses can yield functional Rous sarcoma virus (RSV) pseudotypes of mammalian leukemia viruses (MaLV). RSV pseudotypes with the envelope properties of six strains of MaLV were produced after mixed infection in avian cells permissive for the replication of both types of virus. RSV pseudotypes with the envelope antigens of xenotropic and ecotropic murine leukemia virus were also obtained by fusion

of mammalian cells producing leukemia virus with avian cells producing RSV; however, RSV(MaLV) pseudotypes were not obtained by MaLV superinfection of RSV-transformed mammalian nonproducer cells. Functional RSV(MaLV) pseudotypes were obtained with both nondefective RSV and RSV defective in envelope antigens, but not with RSV that is defective in RNA-directed DNA polymerase. (17 refs.)

- 77-0218 **Replication of Mouse Mammary Tumor Virus in Tissue Culture. II. Kinetics of Virus Production and the Effect of RNA and Protein Inhibitors on Viral Synthesis.** (Eng.) Sarkar, N. H. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave. New York, NY 10021) Pomenti, A. A.; Dion, A. S. *Virology* 77(1): 31-44; 1977.

An analysis of RNA species in purified mouse mammary tumor virus (MuMTV) derived from cultured mouse mammary tumor cells (MuMT-73) showed that the virions harvested soon after the addition of ³H-uridine contained 65S-70S, 42S, 30S-35S, 20S-22S, and 4S RNA's. The 70S and 35S species of RNA were found to be virus-specific by molecular hybridization using radioactive MuMTV-complementary DNA as a probe. Two to 4 hr lapsed between the addition of ³H-uridine and the initial release of virions containing labeled 70S and 35S. Incubation of the cells with actinomycin D completely inhibited viral RNA synthesis within 1 hr, whereas synthesis of viral proteins and the release of mature virions continued for at least 10 hr. The protein composition and architecture of the virus particles produced by the treated and untreated MuMT-73 cells were identical. Exposure of cells to puromycin or cyclohexamide inhibited the replication of MuMTV, but induced the production of an endogenous C-type virus. (35 refs.)

- 77-0219 **Surface Structure of Virions Budding from L1210(V) gln- Mouse Leukemia Cells.** (Eng.) Demsey, A. (Memorial Sloan-Kettering Cancer Center, Walker Lab., Rye, NY) Calvelli, T. A.; Kawka, D.; Stackpole, C. W.; Sarkar, N. H. *Virology* 75(2): 484-487; 1976.

The surface structure of virions budding from L1210(V) gln-murine leukemia cells [a subline of L1210(V) that requires glutamine for growth] was studied by freeze-drying intact cells and examining them by electron microscopy. Three labeling experiments were done using hybrid antibodies: (1) labeling for murine mammary tumor virus (MuMTV) spike glycoprotein; (2) labeling for murine leukemia virus (MuLV) knob glycoprotein; and (3) double-labeling for MuLV and MuMTV surface components on L1210(V) gln- cells. Two types of virus particles were detected, one with random 10-nanometer (nm) surface projections, similar to viruses on cells producing only MuLV, and one with regularly arranged 5-nm projections, similar to budding viruses on cells producing only MuMTV. The results of the double-labeling experiments agree with the indication that individual viral envelopes on L1210(V) gln- cell viruses are homogeneous in their surface structure. The mechanism that draws together

the surface glycoproteins during budding appears, therefore, to be highly specific. (20 refs.)

- 77-0220 **Structural Components of Mouse Mammary Tumor Virus. I. Polypeptides of the Virion.** (Eng.) Yagi, M. J. (Dept. Microbiology, Univ. Alabama Medical Center, Birmingham, AL 35294) Compans, R. W. *Virology* 76(2): 751-766; 1977.

Twelve polypeptides associated with mouse mammary tumor virions (mMTV), 4 major polypeptides and 6-8 minor proteins were analyzed. Three of the major proteins, with estimated molecular wts of 37,000, 52,000, and 60,000, are glycoproteins (gp). Labeling with ^{35}S -sulfate revealed significant amounts of sulfate covalently linked with gp60 and gp52. Variations in the polypeptide pattern of mMTV were observed when virions were grown and labeled under different culture conditions. The virions were morphologically unaltered after incubation with protease; however, both gp60 and gp52 were absent from the polypeptide patterns. These results indicate that cleavage of gp60 and gp52 is possible during ingestion and digestion of mothers' milk by neonatal mice, and therefore, even if cleavage is not necessary for infectivity of the particle, it may not interfere with infectivity in vivo. (32 refs.)

- 77-0221 **Precursor-Product Relationship Between Nonglycosylated Polypeptides of A and B Particles of Mouse Mammary Tumor Virus.** (Eng.) Tanaka, H. (Inst. Virus Res., Kyoto Univ., Kyoto, Japan) *Virology* 76(2): 835-850; 1977.

In a comparative study of various intracytoplasmic particles of mouse mammary tumor virus, sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed that B particles consisted of three major nonglycosylated polypeptides of varying molecular wt and six glycopeptides. All A-particle polypeptides were nonglycosylated. The polypeptide composition of A particles was different from that of B particles. The only common major component was band p7 and three other bands of variable amounts, p43, p37, and p13. After incubation at 37 C for 20 hr, A particles showed a change of pattern; major bands disappeared except for A-p43, A-p37 and A-p7, and a strong new band, A-p25, appeared. No ultrastructural alteration was observed. This conversion was inhibited by diisopropylfluorophosphonate. When purified in the presence of phenylmethanesulfonyl fluoride, A particles consisted of a single major polypeptide, A-p70. Incubation of these A particles resulted in generation of A-p15 in addition to A-p25 and A-p7 at the sacrifice of A-p70. These studies plus studies of antigens indicate that the three major internal components of B particles are generated from a common precursor, A-p70, through enzymatic cleavage and, hence, that A particles are the real pronucleocapsids of B particles. (55 refs.)

- 77-0222 **Presence of the p27 Antigenicity and Absence of the gp52 Antigenicity and Leukemia Virus Antigens in Intracytoplasmic A Particles (iAp) of Mouse Mammary Tumor Origin.** (Eng.) Zotter, S. (Medizinische Akademie "Carl Gustav Carus," Pathologisches Institut DDR-8019 Dresden, Fetscherstr. 74, E. Germany) Kryukova, I. N.; Bukrinskaya, A. G.; Lezhnewa, O. M.; Ilyin, K. V.; Miller, G. G.; Muller, M. *Arch Geschwulstforsch* 46(8): 621-629; 1976.

The absence of the gp52 antigenicity and leukemia virus antigens and the presence of the p27 antigenicity in mouse mammary tumor intracytoplasmic A particles (iAp) were assessed. The mammary tumors contained large A particle clusters and almost no mature type B viruses. On tissue slices of the tumors, some of the sera tested gave a characteristic granular intracellular fluorescence reaction. The A type fluorescence reaction resulted from the labeling of intracytoplasmic A particle clusters. No diffuse cytoplasmic fluorescence was found. Almost no type B fluorescence reaction occurred. The following sera gave strong type A reactions: anti-iAp, anti-p27, and anti-B2792. A moderate type A reaction was given by anti-B65. No type A fluorescence was observed in tests performed with anti-gp52, rat anti-Gross leukemia virus, and anti-Moloney sarcoma virus. By double-gel immunodiffusion, anti-iAp, anti-p27, and anti-B2792 identically detected one antigen of iAp that was immunologically related to the p27 of B particles. The p27 antigen was precipitated in iApCBA and iApC3H by both anti-p27 and anti-iAp. The glycoprotein gp52 of B particles isolated by differential and sucrose density gradient centrifugation from CBA/Blm mammary tumors was identically precipitated by anti-gp52, anti-B2792, and anti-B65. Gp52, immunologically different from p27, was not detectable in iAp. Anti-iAp did not react with gsl (p30) leukemia virus group-specific antigens. The absence of leukemia virus antigens, as determined by immunodiffusion and immunofluorescence, confirms the assumption that iAp of mouse mammary tumor origin are not related to type C viruses. (23 refs.)

- 77-0223 **Gross-Virus-Induced Lymphoma in the Rat. IV. Cytotoxic Cells in Normal Rats.** (Eng.) Shellam, G. R. (Dept. Microbiology, Perth Medical Centre, Shenton Park 6008, Western Australia) *Int J Cancer* 19(2): 212-224; 1977.

Cell suspensions of various lymphoid tissues from normal 8- to 10-wk-old W/Fu rats were preincubated alone at 37 C or 4 C for 3 hr, before washing and testing in the ^{51}Cr release test. Natural cytotoxicity was found predominantly in the spleen, with low but significant levels also in the lymph nodes and blood. Preincubation at 37 C significantly augmented cytotoxicity without altering the relative distribution. However, thymus, bone marrow cells, and thoracic duct lymphocytes were not cytotoxic, even after preincubation. A similar distribution of natural cytotoxicity was noted in cell transfer studies in which irradiated recipients received 10^5 W/FuG-1 cells id alone or mixed with a range of doses of

normal spleen, lymph node, or thymus cells from 10-wk-old W/Fu donors. Cytotoxicity by normal lymphoid cells was less with in vivo than in vitro passaged target cells. Histocompatibility at the major Ag-B locus was not required for target cell - killer cell interaction. The normal spleen cells of many Ag-B genotypes were cytotoxic for W/FuG-1 target cells. It appears that the target specificity of natural cytotoxic cells is an antigen or at least a cell surface structure associated with infection by C-type viruses. (34 refs.)

77-0224 A Possible Requirement for Protein Synthesis Early in the Infectious Cycle of the Murine Sarcoma-Leukemia Virus. (Eng.) Salzberg, S. (Dept. Life Sciences, Bar-Ilan Univ., Ramat-Gan, Israel) Robin, M. S.; Green, M. *Virology* 76(1): 341-351; 1977.

Mouse 3T6 cells were treated with cycloheximide early after infection with Harvey murine sarcoma-leukemia virus [H-MSV(MLV)] to test whether early inhibition of protein synthesis would affect the subsequent formation of viral RNA and virus particles. Virus-specific RNA synthesis and infectious particle production were inhibited reversibly, and these effects were most pronounced when the drug was applied 2-4 hr after infection. Hybridization to a labeled viral DNA probe indicated that nearly half of the intracellular virus-specific RNA cosedimented with cellular polyribosomes 3 hr after infection. This RNA was derived from parental viral genomes, since the same amount of viral RNA was detected in polyribosomes in the presence of arabinosyl cytosine, which prevents viral DNA synthesis and the subsequent transcription of new viral RNA. The binding of parental viral RNA appeared to be specific, since viral RNA was released from polyribosomes following treatment with EDTA. These findings suggest that the MSV(MLV) genome may function as messenger for the synthesis of one or more virus-specific proteins early after infection. They do not exclude the alternative possibility that cycloheximide inhibits some cellular function needed for viral reproduction. Several possible functions for early proteins are suggested: (1) a ligase activity responsible for maturation of the viral DNA molecule; (2) a protein involved in the transport of DNA from the cytoplasm into the nucleus; (3) a protein required for the integration of viral DNA into the cellular genome; and (4) a virus-specific DNA-directed RNA polymerase or polymerase subunit. (26 refs.)

77-0225 Saturable and Nonsaturable Process of Sugar Uptake: Effect of Oncogenic Transformation in Transport and Uptake of Nutrients. (Eng.) Hatanaka, M. (NCI, Frederick Cancer Res. Center, Fort Detrick Building 560, NIH, Frederick, MD 21701) *J Cell Physiol* 89(4): 745-750; 1976.

The influence of oncogenic transformation in the transport and uptake of nutrients was studied. The Harvey strain of mouse sarcoma virus (H-MSV) was propagated and titrated

on secondary cultures of a NIH Swiss mouse embryo tissue culture. Exponentially growing cultures (3×10^5 cells/60-mm plastic petri dish) were infected with H-MSV (10^5 focus-forming units/plate). These cells demonstrated a greatly enhanced rate of sugar uptake compared to uninfected cells. This change occurred with the first appearance of morphological changes in the infected cells and appeared dependent on the transforming process. The uptake of D-glucose, D-mannose, and D-galactose by these cells was consistently greater than that of control cultures over a broad range of initial extracellular concentrations (10^{-7} to 10^{-1} M). However, the wide difference of uptakes decreased at $> 5 \times 10^{-3}$ M. This trend continued after completion of transformation. Nevertheless, at 5×10^{-3} M, the uptake rates of the three sugars by mouse cells were over 50 times faster than a diffusion rate of L-glucose at the same concentration. In addition, 3-O-methyl-D-glucose was taken up at least 100x faster than L-glucose, and 2-deoxy-D-glucose was taken up by chicken cells approx 70x faster at 3×10^{-3} M and over 40x faster at 4×10^{-2} M than L-glucose. Nonsaturable sugar uptake by the cells during and after transformation revealed slight but consistent enhancement compared to controls, and the degree of difference became less at higher sugar concentrations. Animal blood and culture media contained approx 5×10^{-3} M of D-glucose, a concentration that appeared to be a transitional point from saturable to nonsaturable uptake. Negative cooperation of nutrient uptake, such as that found in bacteria, may be involved. (19 refs.)

77-0226 Comparison of Sequence Homology of Poly(A) and Non-Poly(A) Containing 34S RNA of AKR Murine Leukemia Virus. (Eng.) Joseph, D. R. (Basic Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701) *Biochem Biophys Res Commun* 74(2): 499-505; 1977.

The 34S RNA subunits of AKR murine leukemia virus (MuLV), fractionated on the basis of the presence or absence of poly(A) regions, were examined for sequence homology. To obtain intact subunits, AKR MuLV 34S RNA was purified by two successive sucrose gradient centrifugations. The ratio of the poly(A)-containing fraction to the non-poly(A)-containing fraction was 2:1. To determine the sequence homology between the poly(A) and non-poly(A) subunits, both fractions were hybridized to AKR MuLV 3 H-complement DNA (cDNA), and the hybrids were assayed by nuclease S₁ and cesium sulfate centrifugation. The poly(A) and non-poly(A) subunits hybridized to 3 H-cDNA to the same extent (80%), with identical CO1/2 (concentration of RNA at 50% hybridization of the cDNA) values. Hybrids of both fractions had identical thermal denaturation curves, with T_m (temperature at which 50% of the hybrid is dissociated) values of 81 C. These results demonstrate that the poly(A)- and non-poly(A)-containing subunits of the AKR genome have identical or very similar base sequences in the heteropolymeric regions. These findings are consistent with a polyploid model of the viral genome, but they do not rule out the possibility that the genome is haploid and that each

population contains molecules with and without poly(A). (22 refs.)

- 77-0227 Leukemogenic Activity of Murine Type C Viruses after Long-Term Passage In Vitro.** (Eng.) Buchhagen, D. L. (Dept. Viral Oncology, Rockefeller Univ., New York, NY) Pincus, T.; Stutman, O.; Fleissner, E. *Int J Cancer* 18(6): 835-842; 1976.

The leukemogenic activity of murine type C viruses following long-term passage in vitro was evaluated. Five-day-old mice were injected ip with Rauscher, Moloney, and Gross viruses obtained from leukemic mouse tissues and from tissue culture cells that had been infected in vitro and then observed for development of leukemias. Mice infected with mouse-passaged Rauscher leukemia virus showed two clusters of mortality: the first cluster was due to rapidly developing erythroblastic leukemia and was fatal 20-40 days postinoculation; the second began approx 80 days postinoculation and resulted from widely disseminated lymphoblastic or lymphocytic leukemia. The lymphocytic neoplasms induced with Moloney and Gross viruses began in the thymus as lymphomas, with subsequent spread to other lymphoid organs. The high percentages of leukemias among the virus-infected mice compared with the low percentages among the untreated colonies and the higher spleen wt in the injected animals compared with controls implicated the viruses as the leukemia-inducing agents. The tissue culture-grown Gross viruses induced lymphocytic leukemias in 42% of injected newborn C3Hf mice, but the Moloney viruses induced leukemias in 94% of injected newborn BALB/c mice. Rauscher viruses injected into young adult or newborn BALB/c mice induced leukemias in 100% of the mice. The tissue culture-derived Rauscher virus was passaged twice through BALB/c mice in an attempt to recover the erythroblastic leukemia activity. No evidence for erythroblastic disease was obtained, and all the injected mice died of lymphoblastic leukemia. Latent periods were of the same duration as those with the tissue culture-passaged Rauscher virus. Mice that were inoculated at 10 wk of age with tissue culture-passaged Rauscher virus died of lymphocytic leukemia but with an additional 50-day delay in onset of death, the first deaths occurring 130 days after injection. It appears that the capacity to induce leukemia is a stable property of murine leukemia viruses. (26 refs.)

- 77-0228 Oncornavirus Gene Expression During Embryonal Development of the Mouse.** (Eng.) Strand, M. (Dept. Molecular Biology, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., New York, NY 10461) August, J. T.; Jaenisch, R. *Virology* 76(2): 886-890; 1977.

The concentration of two proteins of endogenous type C oncornavirus origin was determined in: (1) mouse embryos isolated during the second half of gestation, (2) newborn mice, and (3) specific organs of adult mice. The two viral proteins

selected were an internal protein of 30,000 daltons molecular wt and an envelope glycoprotein of 70,000 daltons. A different pattern of protein expression was seen in each mouse strain studied. BALB/c tissues had a very low level (< 1 nanogram/mg protein) of both proteins in early embryos and adult tissues, but moderate levels of both were present in late embryos and newborn animals. C3H tissues contained high concentrations of the glycoprotein in embryos and increased concentrations in the newborn and the adult spleen; low levels of the internal protein were present at all stages. AKR mice contained minimal amounts of the glycoprotein in embryos, increased concentrations in the newborn, and high levels in the adult spleen. The internal protein was present at low levels throughout embryogenesis and in the newborn and rose to high levels in the adult spleen. No support was found for the concept that oncornavirus gene expression plays an important role in mammalian embryogenesis. (17 refs.)

- 77-0229 Genetic Factors Influencing Mouse Type-C RNA Virus Induction by Naturally Occurring B Cell Mitogens.** (Eng.) Phillips, S. M. (Dept. Medicine, Allergy and Immunology Section, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19104) Stephenson, J. R.; Aaronson, S. A. *J Immunol* 118(2): 662-666; 1977.

The effects of lipopolysaccharide (LPS) on xenotropic C-type virus release by lymphoid cultures of various inbred murine strains were studied. Virion-associated reverse transcriptase activity was elicited from cultures of each strain examined [AKR/J, Balb/cN, C57BL/6N, CBA/N, C3H/HeJ, C3H/HeN, C3H/FN, DBA/2N, NIH Swiss/N, NZB/N, SWR/J, 129/J, (CBA/N \times DBA/2N) F_1 , and Nu/Nu congenitally athymic mice]. The results indicate that class III as well as class II endogenous viruses can be released in response to LPS. LPS-mediated virus release primarily involved the β lymphocytes; virus release was also efficiently stimulated by other naturally occurring B-cell mitogens, including No-cardia water-soluble mitogen and purified protein derivative of tuberculin (PPD). It is suggested that these agents act synergistically with halogenated pyrimidines, but not with each other, to cause virus release and that B-cell mitogens release virus by a mechanism that differs from that of halogenated pyrimidines. Naturally occurring B-cell mitogens may have use in the detection of evidence of endogenous viruses in species from which such viruses have not as yet been obtained. (26 refs.)

- 77-0230 Effect of a Rauscher Leukemia Virus Vaccine upon Chemical Oncogenesis in the Mouse.** (Eng.) Basombrio, M. A. (Academia Nacional de Medicina, Las Heras 3092, 1425 Buenos Aires, Argentina) *Arch Geschwulstforsch* 46(8): 630-633; 1976.

The influence of a Rauscher leukemia virus vaccine on chemical oncogenesis in the BALB mouse was investigated. The inactive virus was emulsified 1:1 with complete Freund's ad-

vant, and 0.5 ml was injected ip into 2-mo-old mice. The efficiency of the vaccine was tested by an ip challenge 43 days later with 0.1 ml of a 7×10^{-3} cell-free dilution of leukemic spleen. For chemical induction of sarcomas, paraffin pellets containing either 64 or 320 μg of 3-methylcholanthrene (MCA) were implanted dorsally sc. The vaccine was prepared by treating the purified virus pellet with 0.1% formalin for 2 wk at 4 C. Immunization with formalin vaccine protected the mice against the development of leukemia, as shown by a decrease in splenomegaly and a significant increase in the number of survivors. A total of 8/12 vaccinated mice survived, compared to 1/12 controls. In two different experiments, similar immunization had no detectable effect upon tumor induction by MCA. The total incidence of sarcomas and the proportion of mice dying were similar in nontreated and in groups vaccinated with either virus or normal spleen. Within 10 mo, a 64- μg dose of MCA induced 65% and 62% tumors in control and vaccinated mice, respectively, and a 320- μg dose induced 100% sarcomas in both groups. The results show that formalin-treated Rauscher leukemia virus, even though it prevents leukemogenesis by the active virus, fails to inhibit sarcoma induction by near-threshold doses of MCA. (9 refs.)

77-0231 Chemical-Viral Co-carcinogenesis: Requirement for Leukemia Virus Expression in Accelerated Transformation. (Eng.) Mishra, N. K. (Microbiological Associates, Bethesda, MD 20016) Pant, K. J.; Thomas, F. O.; Price, P. J. *Int J Cancer* 18(6): 852-858; 1976.

Chemical-viral cocarcinogenesis is evaluated. Relatively little cytotoxic effect was evident when F111 cells were treated with 1 $\mu\text{g}/\text{ml}$ ethidium bromide (EtBr). Some degree of cytotoxicity was manifested by a slower growth rate, altered morphology, and the appearance of intracellular refractile bodies. The F111 cells dually treated with 4-nitroquinoline-N-oxide (4-NQO) and Rauscher leukemia virus produced soft agar colonies at the second and third subcultures after carcinogen treatment, but infection with virus alone or 4-NQO treatment without concomitant virus infection failed to transform these cells. In both short and long schedules of EtBr treatment, virus-treated cells behaved like control uninfected cells, and transformation could not be detected with either 0.1 or 0.5 $\mu\text{g}/\text{ml}$ 4-NQO, with one exception; at 0.5 $\mu\text{g}/\text{ml}$, 4-NQO-treated cells (EtBr, long series) showed a number of small colonies in agar, in spite of the presence of EtBr during virus treatment. Cyclohexamide (2.5 $\mu\text{g}/\text{ml}$) inhibited 78% of the total cellular protein synthesis and over 99% of virion-associated polymerase in the media during antibiotic treatment. This effect, however, was reversible. A comparable degree of reversible inhibition of viral and cellular protein synthesis was also induced by puromycin (1 $\mu\text{g}/\text{ml}$). A significant amount of total cellular and virus-specific protein synthesis and intact virus production, as measured by virion-associated DNA polymerase assay, was inhibited during 4-NQO treatment by cyclohexamide or puromycin. It is postulated that a virus-specific protein must be expressed during

4-NQO treatment for cocarcinogenic transformation. The presence of EtBr under conditions that prevent virus integration and expression or inhibition of viral protein synthesis by puromycin and cyclohexamide inhibits cocarcinogenesis. (18 refs.)

77-0232 Localization of a Murine Oncornavirus 15,000-Dalton Virion Protein on the Membrane of Neoplastic Cells: Analysis by Immunofluorescence and Immunoelectron Microscopy. (Eng.) Lejneva, O. M. (Lab. Tumor Immunochimistry and Diagnostics, N. F. Gamaleya Inst. Epidemiology and Microbiology, Acad. Medical Sciences USSR, Moscow, USSR) Abelev, G. I.; Dorfman, N. A.; Strand, M.; August, J. T. *Virology* 75(2): 281-292; 1976.

The cellular expression of proteins analogous to the Rauscher virus p15 was examined by immunofluorescence and immunoelectron microscopy. Membrane fluorescence with anti-Rauscher p15 serum was obtained with Balb/c normal spleen cells, Rauscher erythroblastosis cells of a Balb/c mouse, and lymphosarcoma cells of a CC57BR mouse. This suggests that a protein analogous to the Rauscher virus p15 is expressed on the membrane of normal spleen cells as well as the tumor cells. Serum absorbed by normal spleen cells no longer reacted with normal cells, but continued to show membrane fluorescence with erythroblastosis and lymphosarcoma cells. Antigenic determinants of protein were present on the membranes of erythroblastosis and lymphosarcoma cells, but they were absent from the membranes of budding or mature virions. Both type- and group-specific determinants of the protein were accessible to antibodies reacting at the cell surface. This viral protein appears to correspond to previously described cell surface antigens of virus-induced murine leukemias. Since details of the morphogenesis of the type C virion are unknown, the basis for expression of virion proteins at the surface of normal and malignant cells is speculative. This expression may have considerable relevance to the host immune response to both virus and cells. (42 refs.)

77-0233 Cell Cycle-Dependent Inhibition of Kirsten Murine Sarcoma-Leukemia Virus Release by Cytochalasin B. (Eng.) Panem, S. (Dept. Pathology, Univ. Chicago, Chicago, IL 60637) *Virology* 76(1): 146-151; 1977.

The cell-cycle dependence of virus maturation was studied by examining the effects of two inhibitors (cytochalasin B, CB, and vinblastine sulfate, VB) of contractile element function on the release of Kirsten murine sarcoma-leukemia virus [KiMSV(KiMuLV)] from chronically infected normal rat kidney cells (NRK-K). CB and VB inhibited KiMSV(KiMuLV) release from logarithmically growing NRK-K cells in a dose-dependent manner. VB also inhibited mitosis and cell division. With 25 $\mu\text{g}/\text{ml}$ CB, mitosis and cell division were not inhibited, whereas virus release was inhibited by at least 70%. Max inhibition occurred within 4.5 hr of adding CB to logarithmically growing NRK-K cells, and inhibition was reversed within 3 hr of drug removal. CB inhibition of

virus release from synchronously growing NRK-K cells was cell-cycle-dependent and occurred during the late G2 phase and mitosis. Electron microscopic examination of CB-inhibited cells did not show an accumulation of budding forms, although cultures released from CB inhibition produced elevated amounts of KiMSV(KiMuLV) shortly after drug removal. These data suggest that virion components accumulate in CB-treated cells prior to visually detectable condensation of KiMSV(KiMuLV) at the plasma membrane. Although virus release ordinarily occurs at the G2/M interphase, the rapid appearance of virus in culture fluids following CB removal from logarithmically growing cells indicates that the final events of virus replication can occur in G1. It is concluded that the event(s) that confers cell-cycle dependency on KiMSV(KiMuLV) replication occurs prior to virus maturation. (22 refs.)

- 77-0234 Detection of Human C-Type "Helper" Viruses in Human Leukemic Bone Marrow with Murine Sarcoma Virus-Transformed Human and Rat Non-Producer Cells.** (Eng.) Nooter, K. (Radiobiological Institute TNO, Rijswijk, the Netherlands) Bentvelzen, P.; Zurcher, C.; Rhim, J. *Int J Cancer* 19(1): 59-65; 1977.

A C-type helper virus for defective murine sarcoma virus (MSV) was demonstrated in leukemic bone-marrow cells by genome rescue and immunofluorescence experiments. Bone marrow cells from two children who had acute lymphoblastic leukemia, when cocultivated with a canine thymus cell line (A7573) showed reverse transcriptase activity. Normal bone marrow cells used as a control gave negative results. A new pseudotype of MSV that transformed rat embryo, rabbit cornea, and human kidney cells was obtained from cocultivation of infected canine cells with MSV-transformed human cells R-970-5 or rat cells K-NRK. Cocultures of control bone marrow had no transforming activity. The focus formation was inhibited by an antiserum to the simian virus, but not by an antiserum to murine leukemia virus. (29 refs.)

- 77-0235 Murine Sarcoma Viruses: The Helper-Independence Reported for a Moloney Variant is Unconfirmed; Distinct Strains Differ in the Size of Their RNAs.** (Eng.) Maisel, J. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, CA 04720) Dina, D.; Duesberg, P. *Virology* 76(1): 295-312; 1977.

A variant of Moloney murine sarcoma virus (Mo-MSV), designated Mo-MSV 124 and reported to behave like a nondefective sarcoma virus, was analyzed to confirm its alleged helper-independence. NRK rat cells were infected with Mo-MSV 124 at a very low multiplicity, and six foci of transformed cells were isolated. Four of these six transformed clones failed to produce virus unless superinfected with helper Mo murine leukemia virus (MLV). The RNA of the parental virus stock was compared electrophoretically to the RNA from the two clones that produced virus after the initial infection (producer clones) or the RNA from the four nonproduc-

er clones. All clones contained a MSV-specific 30S RNA species. In addition, virus from one producer clone also contained 38S MLV RNA at a high concentration, indicating that the original stock must have contained such a species. It is suggested that Mo-MSV 124 is defective and contains helper leukemia virus at a low concentration. This would explain the ready generation of nonproducer clones by infection at low multiplicity, the difficulty in detecting 38S MLV RNA in the original virus stock, and the low size ($1.8-1.0 \times 10^6$ daltons) and complexity of the 30S Mo-MSV 124 RNA. These results are compatible with the properties of a defective MSV genome but incompatible with those of a nondefective MSV genome. The MSV-specific RNA components of different clonal isolates of Mo-MSV differed from each other in size, ranging between 2.1 and 1.6×10^6 . The sarcoma- or transformation-specific RNA components of all transforming viruses tested were smaller than the 38S RNA of helper leukemia viruses (3.1×10^6). This is consistent with the notion that the MSVs described are defective, lacking the genetic information present in the larger RNA genomes of self-replicating MLVs. (56 refs.)

- 77-0236 Murine and Simian C-Type Viruses: Sequences Detected in the RNA of Human Leukemic Cells by the C-DNA Probes.** (Eng.) Tavitian, A.; Larsen, C. J.; Hamelin, R.; Boiron, M. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 451-455; 1976.

Molecular hybridization with two synthetic complementary DNA (c-DNA) probes was used to detect virus-like sequences in the RNA of human acute and chronic leukemias. The c-DNA probes were synthesized with the murine sarcoma-leukemia viruses (Moloney Isolate) (M-MSV-MLV) produced continuously by the transformed rat cell line 78A-1. A simian probe was synthesized with the simian (Woolly Monkey) sarcoma and simian sarcoma-associated viruses (SSV) produced by the Normal Rat Kidney (NRK) cell line. There was a strong correlation between the two probes with regard to the positivity or negativity of hybridization to human cellular RNA. An acute myeloblastic leukemia, which revealed a negative cellular RNA hybridization with the murine M-MSV-MLV c-DNA probe, showed a positive annealing of its RNA with the SSV c-DNA probe (4.5% hybridization rate); this was also the case for one acute lymphoblastic leukemia (ALL) which gave the highest rate of hybridization (14.5%) with the SSV probe. In contrast, another ALL was completely negative with the SSV c-DNA probe but was slightly positive (4.8%) with the M-MSV-MLV probe. Cross hybridization experiments revealed that there was at most 10% homology between the two viruses. The c-DNA common to both viral genomes was isolated after alkaline digestion of the hybrids; it was not possible to hybridize this c-DNA to the RNA of an ALL which was highly positive when the entire c-DNA probes of both SSV and M-MSV-MLV were used for the annealing tests. Examination of the associa-

on rates of simian and murine c-DNA to sheared cellular DNA of various origins revealed that SSV virus produced in FRK cells contains a much higher percentage (100%) of rat sequences as compared to the percentage of rat sequences (15.3%) in the M-MSV-MLV viruses that are produced in the 78 A-1 rat fibroblast cell line. In contrast, the proportions of human spleen (10%) and mouse embryo (42% to 44%) sequences were comparable in both viruses. The sequences detected in human RNA from leukemic cells are thus completely different when the simian or murine c-DNA probe is used for the hybridization. Moreover, the c-DNA portion homologous to both virus genomes cannot detect any virus-related sequences in the RNA of leukemic cells, even though it can form stable hybrids with rat cellular DNA. (9 refs.)

77-0237 Relationships Between H-2 and Viral Antigens in Murine Oncornvirus-Induced Tumours. (Eng.) Gomard, E. (Batiment Gustave Roussy, 7eme etage, 17 rue du Faubourg Saint Jacques, F75014 Paris, France) Duprez, V.; Henin, Y.; Levy, J. P. *J Immunogenet* 4(1): 35-5; 1977.

Cytotoxic T lymphocytes (CTL) from murine sarcoma virus (MSV) or Friend leukemia virus (FLV)-inoculated mice lysed syngeneic FMRGi+ (Friend, Moloney, Rauscher, or Graffi) lymphoma cells much more efficiently than allogeneic FMRGi+ lymphoma cells. The cytolysis of various H-2 antigen-different ⁵¹Cr lymphomas was composed by the CTL from several inbred and congenic lines differing at H-2 and by competition experiments using unlabeled cells. The results indicate that this phenomenon is due to an H-2 barrier. H-2b/I-2d hybrid-anti-MSV-CTL immunized by H-2b, H-2d, or H-2b/H-2d tumors lysed only FMRGi+ lymphomas of the same H-2-identical competitive cells. This indicates that H-2 antigens are directly involved in the interaction between tumor cells and immune CTL that probably react with an H-2 modified antigen on the tumor cell surface. The use of CTL from intra-H-2 recombinant lines shows that H-2D and probably H-2K molecules are involved, but they vary according to the tumor cells. It could not be determined if the I region plays a role in the CTL/tumor cell interaction. The possible effects of Ia antigens due to I-A and I-B subregions cannot be excluded in the combinations tested. It is concluded that restriction of the cytolysis of tumor cells by anti-MSV-CTL and anti-FLV-CTL is related to H-2 antigens. These antigens could play a major role in immunosurveillance against oncogenic and nononcogenic viruses and against viral tumors. (23 refs.)

77-0238 In Vitro Replication of RNA Tumor Viruses. (Eng.) Haseltine, W. A.; Baltimore, D. In: *Annual Virology. ICA-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. New York: Academic Press, Inc.; Vol. 4, pp. 175-213; 1976.

The initiation and elongation of DNA synthesis of the RNA tumor viruses are examined, and a model for RNA tumor virus replication is proposed. In vitro synthesis of DNA by

the DNA polymerase found in virions of RNA tumor viruses is a primer-dependent reaction, and 90% of the DNA molecules copied from 70S RNA are initiated using transfer RNA (tRNA)-Trp as the primer. The observations that a specific tRNA molecule serves as a primer and that this RNA is hydrogen-bonded to the 35S RNA suggested that the primer directs the polymerase to the correct initiation site or sites. The growing DNA chain was found to elongate continuously along a unique sequence of viral RNA. This observation, coupled with the finding that in Rous sarcoma virus the site of DNA initiation is located near the 5' end of the genome, implies that the polymerase somehow continues the extension of DNA by switching to the 3' end of the RNA. A model is discussed that proposes that there is a common sequence at the 3' and 5' ends of the genome (exclusive of the poly A sequences). There is also a sequence located near the 5' end that is antiparallel and complementary to the redundant sequence and a different set of antiparallel complementary sequences located internally near the 5' end of the genome. This model is called the site-specific integration model of RNA tumor-virus replication. (24 refs.)

77-0239 Murine Sarcoma Virus (MSV)-Induced Tumors in Mice. I. Distribution of MSV-Immune Cytolytic T Lymphocytes In Vivo. (Eng.) Plata, F. (Unit Human Cancer Immunology, Lausanne Branch, Ludwig Inst. Cancer Res., Lausanne, Switzerland) Sordat, B. *Int J Cancer* 19(2): 205-211; 1977.

Murine sarcoma virus (MSV) tumors were induced in female, inbred, C57BL/6 mice by intraperitoneal injection of a cell-free virus homogenate of the Moloney murine sarcoma and leukemia complex. Rauscher virus-induced RBL-5 (H-2b) lymphoma cells were used as syngeneic target cells in the ⁵¹Cr-release assay. Moloney virus-induced LSTRA (H-2d) cells were used as allogeneic tumor target cells in some experiments, and EL4 (H-2b) leukemia cells and P-815-X2 (H-2d) mastocytoma cells were used as control target cells in some cytotoxicity assays. Various lymphoid organs, including the spleen, mesenteric lymph nodes (MLN), and lymph nodes regional to the tumor (RLN) and peripheral blood leukocytes (PBL) were studied. In addition, the kinetics of appearance of cytolytic cells within the MSV-induced tumor was determined. The cytotoxicity tests showed that there were high numbers of cytolytic cells in the spleen, RLN, and PBL between days 7 and 9 after MSV injection (ie, the time of max tumor development). The highest cytolytic activity was among PBL on day 9, with spleen cells showing somewhat less activity. RLN cells showed max activity on day 7. Low activity was detected in MLN cells. On day 12, the highest number of cytolytic cells was found among the tumor cells, at the onset of tumor regression. A second peak of activity occurred around day 21 with PBL, RLN, and spleen cells. Immunofluorescence studies showed that both B and T lymphocytes were present among the tumor cells. The enhanced cytolytic activities of intratumoral lymphocytes, as well as their cytostatic effect on tumor cell growth, suggest that the cell-mediated immune response to MSV tumors might play an important role in tumor rejection. (29 refs.)

77-0240 Effect of Friend Leukemia Virus on Megakaryocytes and Platelets in Mice. (Eng.)

Brown, W. M. (Div. Histology, Dept. Anatomy, Faculty Medicine, Univ. Toronto, Toronto, Canada) *Int J Cancer* 18(6): 764-773; 1976.

The influence of Friend leukemia virus (FV) on platelets and megakaryocytes in C3H/Bi mice was assessed. The number of megakaryocytes in the femoral bone marrow of infected mice was lower than that in controls at 3 days and declined to less than one-third of control values by day 11. In the spleens of infected mice, the number of megakaryocytes was lower than that in controls at 5 days, and the decline continued to day 11, at which time the total number in the spleen had reached a level that was one-third of that in controls. A decline in both the relative and absolute numbers of megakaryocytes was demonstrated in bone marrow and spleen. The bone marrow tended to become hypocellular with time; the spleens became hypercellular after infection. Circulating blood platelets decreased in number between 6 and 9 days after FV infection. Infection with 300 and 3,000 focus-forming units (FFU) FV resulted in a reduction in the number of marrow megakaryocytes at 3 days; this was followed 6 days later by a decrease in the number of circulating platelets. Cells from femoral bone marrow of control and FV-infected (1,000 FFU) mice 9 days after injection were subjected to velocity sedimentation at unit gravity. In marrow from FV-infected mice, there was a distinct decrease in 16C DNA and a total absence of 32C DNA megakaryocytes. Megakaryocytes of 8C DNA appeared to be relatively but not absolutely increased in number in these animals, and 4C megakaryocytes were relatively and perhaps also absolutely increased. Virus infection may lead to preferential elimination of those megakaryocytes in the higher DNA classes and/or may interfere with the normal sequential doubling of the DNA content of megakaryocytes. (22 refs.)

77-0241 Selective Incorporation of H-2 Antigenic Determinants into Friend Virus Particles. (Eng.)

Bubbers, J. E. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY 10461) *Nature* 266: 458-459; 1977.

The incorporation of H-2 antigenic determinants into Friend virus (FV) particles was investigated. Serum collected from mice infected 10-14 days previously with a high dose of NB-tropic FV was the source of virus. After clarification of the serum at $6,800 \times$ gravity, virus was pelleted by centrifugation at $100,000 \times$ gravity. The pellet was resuspended in buffered saline containing detergent (Nonidet P-40, 0.25%) to disrupt the virus. The preparation was tested for its capacity to inhibit the complement-mediated lysis of uninfected (BALB/c \times BALB.B) F_1 lymph node target cells with antisera monospecific for either H-2Kb, H-2Db, H-2Kd, or H-2Dd antigenic specificities. Only lysis by anti-H-2Db antiserum [(A \times HTI) F_1 anti-EL4; H-2a/H-2i anti-H-2b] was detectably inhibited. An identical pattern of inhibition was seen with a second anti-H-2Db antiserum (BALB/c anti-BALB.G; H-2d anti-H-2g) raised against normal spleen cells rather than EL4

tumor cells. Similarly, in virus grown in (C57BL/6 \times DBA/2) F_1 mice, which were also H-2b/H-2d heterozygotes with a different genetic background, H-2Db alloantigen but not H-2Kb, H-2Kd, or H-2Dd was detected. The inclusion of H-2 antigens in virus particles is concluded to be selective rather than random. (10 refs.)

77-0242 Immunoprecipitation of Murine Leukemia Virus-Specific Polyribosomes: Identification of Virus-Specific Messenger RNA. (Eng.)

Mueller-Lantz, N.; Hatlen, L.; Fan, H. In: *Animal Virology. ICN-UNESCO Symposia on Molecular and Cellular Biology*. Baltimore, Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Vol. 4, pp. 37-53; 1976.

An antiserum monospecific for the internal structural protein p30 of Moloney murine leukemia virus (M-MuLV) was used to immunoprecipitate the polyribosomes synthesizing viral protein from producer cells. Approximately 7% of the virus-specific mRNA in purified polyribosomes was recovered after immunoprecipitation, while normal serum precipitated 10-fold less. Size analysis of the virus-specific mRNA in immunoprecipitated polyribosomes indicated that it was 35S in size. These experiments indicate that a subset of cellular M-MuLV-specific mRNA's coding for internal structural proteins can be isolated. (18 refs.)

77-0243 Rapid Screening Assay for Revertants of Murine Sarcoma Virus-Transformed Cells. (Eng.)

Nomura, S. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20014) *Methods Cell Biol* XIV: 229-236; 1976.

A rapid screening assay for revertants of murine sarcoma virus (MSV)-transformed cells is presented. Reversion frequency was tested in two sublines of 3197, 3-321 and 3-36 in the Ki-BALB line, and in S+L- revertants retransformed by MSV. All cell cultures were grown and maintained after virus infection in modified McCoy's 5a medium with 10% fetal calf serum. Cells were infected in suspension with murine leukemia virus (MuLV) at a multiplicity of infection (moi) of over five focus-inducing units (FIU) per cell, 1,000,000 cells in 5 ml of medium were delivered into 25-cm² flasks, and the flasks were incubated at 37 C. After 4 days, the flasks were shaken to detach the relatively loose cells which were removed in the supernatant. Cultures were washed twice with medium and then refed with 5 ml of fresh medium. After a further 3-4 days of incubation, flat, contact-inhibited revertant cell colonies formed that were then counted. When S+L- cells were infected with MuLV at high moi (> 5 FIU), MSV was rescued from them approx 12 hr after infection. At that time, rescue-negative revertant cells underwent MuLV infection, viral interference developed, and no transformation of revertants was possible by the rescue MSV. Revertants remained flat and formed colonies. The rapid screening assay allowed detection of revertant colonies in mixed populations containing a large excess of transformed cells. The procedure is not only useful for the determination

of the spontaneous reversion frequency in MSV-transformed cells, but also for studying the reversion effects of physical, chemical, and biological agents that enhance the frequency of reversion. (13 refs.)

- 77-0244 **A Structural Protein Complex in Moloney Leukemia Virus.** (Eng.) Leamson, R. N. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104) Shandler, M. H.; Halpern, M. S. *Virology* 76(1): 437-439; 1977.

An investigation was conducted to determine whether disulfide bonds might exist between certain proteins of Moloney murine leukemia virus (M-MuLV). For structural analyses, M-MuLV was propagated in MJD 54 cells. To detect the possible presence of disulfide bonds between viral proteins, a purified preparation of ^3H -leucine-labeled virus was divided into two parts, and electrophoretic mobility was determined under reducing and nonreducing conditions. The results indicated that a fraction of the gp69/71 glycoprotein is disulfide-linked to a second, small, nonglycosylated protein in the assembled virion. Under nonreducing conditions, approximately 0%-60% of the gp69/71 was shifted to a different electrophoretic peak. Whether this means that some gp69/71 is not disulfide-bonded in intact virions or that the bond is labile, allowing spontaneous reduction to occur, is undetermined. It is speculated that gp69/71 is disulfide-linked to p15(E), a surface component of M-MuLV having a slightly lower electrophoretic mobility than p15-p12. It was previously reported that gp69/71 and p15(E) are cleavage products of a common precursor. A disulfide bond between such cleavage products raises the question of the sequence of events occurring during the synthesis, maturation, and final incorporation into virus of these two components. It is possible that more than one distinct viral protein is disulfide-bonded to gp69/71 or that alternate termination of cleavage points gives rise to several forms of essentially the same protein. (9 refs.)

- 77-0245 **Biological Properties of Cell Lines Derived from Moloney Virus-Induced Sarcoma.** (Eng.) Di Marco, A. (Div. Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy) Pasadia, T.; Giuliani, F.; Necco, A.; Casazza, A. M.; Mora, L. T.; Luborsky, S. W.; Waters, L. *Tumori* 62(4): 415-428; 1976.

The biological properties of two cell lines derived from Moloney virus-induced sarcoma in a BALB/c mouse were investigated. The MS-2 cells were checked for overgrowth potential at the 21st tissue culture transfer. Upon injection into syngeneic mice, they produced progressively growing tumors that proved lethal to 100% of the animals within 30 days. These tumors were classified as malignant sarcomas. They were transplanted by im inoculation of BALB/c mice (MS-2 tumors). The MS-2 tumors maintained the characteristics of progressive growth for more than 90 in vivo passages. A fur-

ther demonstration of the higher malignancy of these tumors was the presence of visible lung metastases. After 17 in vivo passages, a tumor was explanted in vitro and a second cell line (MS-2T) was established. The MS-2 and the MS-2T cell lines were serially transferred in tissue culture. The MS-2 cell line produced nonregressing tumors at the 21st transfer. After further transfers, its malignancy decreased, as demonstrated by tumor regression. The MS-2T cell line gave 100% nonregressing tumors in BALB/c mice at the 11th transfer. An im injection of these cells at a dose of 10^6 cells produced nonregressing tumors up to the 30th transfer. The MS-2 line, up to the 46th transfer, was composed predominantly of large epitheliallike cells that often overlapped, but the MS-2T cell line up to the 25th transfer showed small regular fibroblasts and rounded cells that were loosely attached. They were also observed floating free in the medium. Judging from the ^3H -uridine incorporation profiles obtained from the media from both cell lines, there was little C-particle production in these cell lines. The immunofluorescence test failed to reveal MSV-M virion antigens on either MS-2 or MS-2T cells. MS-2T cells showed a pattern of reactivity depending on the number of in vitro transfers. Serum of mice with MS-2 tumors reacted with MS-2T cells when they produced progressive tumors. The MS-2 cells at the 49th transfer specifically reacted with serum from mice immunized by repeated injections of MS-2T cells at the 64th transfer. Antigens different from the MSV-M antigens were present on the cell lines, and antigenic changes occurred with increased number of transfers. Chromosomal analysis of MS-2 cells at the 21st transfer showed a modal number of 48 and at the 46th transfer a modal number of 60. The modal number of MS-2T cells at the 25th transfer was 44. The results show that malignancy decreases as the number of transfers increases. (20 refs.)

- 77-0246 **Lymphoma Associated with an Epizootic of Lymphocytic Choriomeningitis in Syrian Hamsters (*Mesocricetus auratus*).** (Eng.) Garman, R. H. (Div. Lab. Animal Medicine, Univ. Rochester Sch. Medicine Dentistry, Rochester, NY 14642) Bowen, G. S.; Fowler, E. H.; Kraus, A. L.; Newman, A. I.; Rifkin, B. R.; Andrews, E. J.; Winkler, W. G. *Am J Vet Res* 38(4): 497-502; 1977.

A hamster-associated epizootic of lymphocytic choriomeningitis (LCM) virus infection was investigated based on necropsies performed on 130 hamsters. Lymphoma appeared to arise in the small intestine, possibly from hyperplastic Peyer's patches that were present in many hamsters. The lymphoma replaced the lamina propria and submucosa and eventually the entire intestinal wall, with resultant necrosis of the mucosal surface. Meningitic infiltrates were most prominent over the cerebellum and caudal part of the cerebrum; they consisted of small lymphocytes, usually with only minimal meningeal thickening. Lymphoreticular interstitial infiltrates in the kidney, as in the liver, varied from small lymphocytes and plasma cells to lymphoblastic and immunoblastic cells. Small- or medium-sized lymphocytes were present in small numbers on organ capsules, the small intestinal serosa, around mesenteric vessels, and in the region of the epididymis

testis. Many small lymphocytes and/or plasma cells were present within the lamina propria or submucosa of the intestine. The frequency of intraabdominal lymphoma was significantly increased in LCM-positive hamsters treated with 7,12-dimethylbenz(a)anthracene. Active virus infection is concluded to be associated with a lymphoreticular infiltrate in the kidney and liver. (25 refs.)

- 77-0247 **RD-114 and Feline Leukaemia Virus Genome Expression in Natural Lymphomas of Domestic Cats.** (Eng.) Niman, H. L. (Dept. Biochemistry, USC Sch. Medicine, Los Angeles, CA 90033) Stephenson, J. R.; Gardner, M. B.; Roy-Burman, P. *Nature* 266(5600): 357-360; 1977.

Gene expression of feline leukemia virus (FeLV) and feline endogenous xenotropic virus (RD-114) at the transcriptional and translational levels in domestic cats was studied in relation to naturally occurring lymphoma. The transcription of virus-specific RNA in the tissues was determined by molecular hybridization. The levels of the 30,000 dalton major structural protein(p30) of both viruses were determined on the same tissues by competition radioimmunoassays. Fifty-five lymphoma tissues from 31 cats and 60 normal control tissues from 47 cats were assayed for the RNA and p30 of RD-114 and FeLV. There was a significantly higher level of RD-114 transcription and translation in most lymphoma tissues compared with normal tissues. In general, only the lymphomas from younger cats showed significant levels of FeLV gene expression [414.0 nanograms (ng) p30/mg cell protein]. RD-114 expression was high in the lymphomas of both young and old cats (48.3 and 59.0 ng p30/mg cell protein, respectively). It is concluded that certain functions of endogenous RD-114 are closely associated with the development of lymphoid tumors in the cat. (27 refs.)

- 77-0248 **Human Papilloma Viruses (HPV): Characterization of Four Different Isolates.** (Eng.) Gissmann, L. (Institut für Klinische Virologie, Universität Erlangen-Nürnberg, Loschgestrasse 7, 8520 Erlangen, W. Germany) Pfister, H.; zur Hausen, H. *Virology* 76(2): 569-580; 1977.

The DNA from 36 human papilloma virus (HPV) isolates from individual human warts were analyzed for cleavage patterns after restriction enzyme digestion with the endonucleases EcoRI, BamHI, Hind II, Hind III, Hpa II, and Hae III. In addition, the electrophoretic mobility of virion proteins from selected isolates was studied by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Four different cleavage patterns were observed: isolates HPV 1, HPV 2, and HPV 3 had many cleavage sites in common (differing only in a few sites), but HPV 4 was entirely different. The electrophoretic mobility of proteins of HPV 4 also differed markedly from those of HPV 1-3. Complementary RNA transcribed from either HPV 1 or HPV 4 did not hybridize with the heterologous isolate. Antiserum reacting with HPV 1-3 failed

to react with HPV 4 antigens. HPV 4 is concluded to represent a new human papilloma virus. Preliminary data suggest that HPV 4 occurs in about 20% of verrucae vulgares with low virus production, but HPV 1, which is representative of about 70% of these papillomas, predominates in warts with high virus yields. (18 refs.)

- 77-0249 **Comparative Primary Structure Analysis of the p30 Protein of Woolly Monkey and Gibbon Type C Viruses.** (Eng.) Oroszlan, S. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD 21701) Copeland, T.; Smythers, G.; Summers, M. R.; Gilden, R. *Virology* 77(1): 413-417; 1977.

Tryptic peptide mapping and NH₂-terminal amino acid sequence analysis covering the initial 28 residues were used to compare the primary structures of the major internal virion protein (p30, approx molecular wt, 30,000) of gibbon (GaLV) and woolly monkey [SSV (SSAV)] C-type viruses. The SSAV sequence was identical with the GaLV sequence through the 28 residues compared. Amino acid sequence comparisons indicate that the major differences in the NH₂-terminal sequence between the p30 of mouse C-type viruses and the p30 of GaLV and SSV (SSAV) are based on a large number of inserted residues in the latter two proteins. (22 refs.)

- 77-0250 **Surface Exposure of Glycosaminoglycans in Resting, Growing and Virus Transformed 3T3 Cells.** (Eng.) Vannucchi, S. (Inst. General Pathology, University of Florence, 50134 Florence, Italy) Chiarugi, V. P. *J Cell Physiol* 90: 503-510; 1977.

Differences in surface glycosaminoglycans (GAGs) between normal and transformed 3T3 cells and between resting and growing 3T3 cells are reported. Cells were labeled with ³H-glucosamine and ³⁵S-sulfate and then incubated with 0.25% trypsin. The trypsinates were isolated and analyzed by AG 1 x 2 chromatography. Elution patterns revealed a large heparan sulfate (HS) peak and a small hyaluronic acid (HA) peak in resting cells. In growing and polyoma virus transformed cells the peak appeared strongly reduced and the HA peak, enlarged. The use of the enzymes hyaluronidase and heparitinase showed that the heparitinase-sensitive radioactivity was higher in resting cells than in either growing cells or transformed cells. Pulse and chase experiments indicated that the turnover of the coat GAGs was higher in the resting cells as compared with either the growing or transformed cells. The differences in the cell coat content of HS and HA are suspected to depend more upon growth than upon transformation. (15 refs.)

- 77-0251 **Cell Cycle Changes in Transformed Cells Growing Under Serum-Free Conditions.** (Eng.) Bush, H. (Dept. Pathology, New York Univ. Medical Centre, New York, NY)

York, NY 10016) Shodell, M. *J Cell Physiol* 90: 573-584; 1977.

SV40 transformed mouse cells (SV3T3) and polyoma transformed hamster cells (PyBHK) transferred in culture using crystalline trypsin followed by treatment with soybean trypsin inhibitor proliferated in serum-free medium. Stock cell cultures were washed twice and then incubated with 1 ml phosphate buffered saline (PBS) containing 0.2 mg crystalline trypsin. Two min later, 2 ml of a 0.25% solution of soybean trypsin inhibitor in PBS plus 2 ml of serum-free Waymouth's medium was added. After obtaining a single cell suspension, the suspension was pelleted, and the supernatant was discarded. The pellet was resuspended in 3 ml of a solution containing 2 ml pre-warmed serum-free Waymouth's medium with or without 1 ml 0.25% soybean trypsin inhibitor. Transformed cells, transferred in this manner, proliferated freely in defined medium without any serum supplement and without any intervening period of adaptation. SV3T3 cells continued to divide for up to 6 days, although at a reduced growth rate. Similar results were obtained with PyBHK cells. Studies on DNA synthesis showed that regardless of growth rate the percentage of cells synthesizing DNA remained constant. The rate of DNA synthesis was proportional to the growth rate. (27 refs.)

77-0252 **Biological Activities of Deletion Mutants of Simian Virus 40.** (Eng.) Scott, W. A. (Dept. Biochemistry, Univ. Miami, Sch. Medicine, Miami, FL 33152) Brockman, W. W.; Nathans, D. *Virology* 75(2): 319-334; 1976.

Mutants of simian virus 40 (SV40) with large deletions in the early or late regions of the genome were tested for biological activity. Two mutants had deletions spanning the two known late genes of SV40 (B/C and D) and had the entire early region intact. Two other mutants had deletions that eliminated 60%-70% of the early region and had the entire late region uninterrupted. The mutants lacking portions of both late genes were able to induce T antigen in infected cells, replicate their DNA in the absence of helper virus, stimulate thymidine incorporation into cellular DNA, and transform mouse and hamster cells. Cells transformed by these late deletion mutants contained the mutant genome, as demonstrated by fusion-complementation rescue procedure. The deletion mutants lacking substantial portions of the early genomic region lacked all of these activities. Both early and late deletion mutants, however, interfered with SV40 DNA replication. The finding that the early genome segment of SV40 DNA is sufficient for viral DNA replication indicates that this segment of DNA will be useful as a vector for constructing self-replicating plasmids containing inserted DNA segments. (39 refs.)

7-0253 **The Role of SV40 Gene A in the Alteration of Microfilaments in Transformed Cells.** (Eng.) Collet, J. J. (Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX 77030) Brugge, J. S.; Noonan, C. A.;

Butel, J. S. *Exp Cell Res* 105(1): 119-126; 1977.

Normal and simian virus 40 (SV40)-transformed cultured mammalian cells were examined by electron microscopy for alterations in the number and distribution of microfilaments associated with viral transformation. Normal hamster embryo fibroblast (HEF) cells and normal Balb-3T3 cells grown at permissive or nonpermissive temperatures contained abundant 50- to 70-A microfilaments along the bottom of the cell and bundles of microfilaments running along the longitudinal axis beneath the plasma membrane, in areas of cell-to-cell contact. In contrast, murine cells transformed by wild-type (WT) SV40 (HaWT-2 and Balb/WT) and grown at either temperature contained fewer microfilaments, as did mouse and hamster cells transformed by tsA mutants and grown under permissive conditions. Under nonpermissive conditions, however, both rodent lines transformed by tsA mutants (Balb/A30 and Ha/A30) assumed a more normal phenotype, with polymerized microfilaments being observed along the bottom of the cells and below the plasma membrane. In simian cells (TC-7), bundles of microfilaments were seen not only in normal cells, but also in WT- and tsA-transformed cell lines, which fail to exhibit classical properties of transformation. These results indicate an association between the expression of a virus-specified function important to the maintenance of the transformed phenotype and the appearance of altered microfilament patterns. (28 refs.)

77-0254 **Tumor-Specific Transplantation Antigen is Expressed During SV40 Lytic Infection with Wild-Type and tsA Mutant Viruses.** (Eng.) Anderson, J. L. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014) Martin, R. G.; Chang, C.; Mora, P. T. *Virology* 76(1): 254-262; 1977.

The expression of simian virus 40 (SV40) tumor-specific transplantation antigen (TSTA) in SV40-infected monkey cells was assayed at permissive and restrictive temperatures using detergent extracts of cell membranes and cytosol to immunize Balb/c female mice prior to an SV40 ascites-tumor challenge. TSTA was expressed during infection of CV-1 monkey kidney cells by wild-type SV40 and by a temperature sensitive (ts) A mutant. The tumor-rejecting capacity induced by the detergent extracts of cell membranes was specific: (1) a non-SV40 tumor line (a methylcholanthrene-induced tumor) was not rejected, and (2) detergent extracts from SV40 but not polyoma-transformed cells were protective. TSTA was induced in wild-type infection and in tsA mutant infection at restrictive and permissive temperatures. A kinetic study demonstrated that TSTA emerges early in the lytic cycle; it is present at 14 but not at 6 hr after infection and then increases several times between 14-26 hr. This parallels the appearance of tumor antigen, as assayed by complement fixation. TSTA, a protein of at least 50,000 daltons, might be either a product of the host cell induced by SV40 or a product of the A gene modified in a distinct fashion from TA but possessing at least partial amino acid homology with TA. (34 refs.)

- 77-0255 **The B/C Gene of Simian Virus 40.** (Eng.) Lai, C. J. (NCI, Bethesda, MD 20014) *Virology* 75(2): 335-345; 1976.

The properties of mutants with deletions in the genome segment of simian virus 40 (SV40), where temperature-sensitive (ts) B, C, and BC mutants map, were investigated. Mutants of SV40 with deletions in this genomic segment were constructed by enzymatic excision of DNA from the viral genome, followed by cloning in the presence of a complementing tsA mutant of SV40. After localization of deleted genome segments by analysis of endo R fragments and electron microscopic heteroduplex mapping, selected deletion mutants were tested for complementation by ts mutants and screened for their ability to produce new viral proteins in infected cells. Complementation tests indicated that B/C deletion mutations are in a cistron distinct from that of tsA and tsD mutations and that the junction between the B/C and D genes is within Hin-K. The B/C gene product was identified by detection and characterization of a short protein present in cells infected with the deletion mutant dl-1010, but not in wild-type SV40-infected cells or in cells infected with different late deletion mutants. This protein precipitated with antiserum against dissociated SV40 virions and had lysine-containing tryptic peptides that cochromatographed with VP1 tryptic peptides. It is concluded that the B/C gene, containing 1,200 nucleotide pairs, codes for VP1. Since deletion mutants lacking Hin-E do not complement B mutants, it is suggested that the Hin-E DNA segment has a signal required for expression of the B/C gene, ie, a promoter or processing signal involved in forming late 16S messenger RNA (the mRNA for VP1) or a ribosome binding site. (29 refs.)

- 77-0256 **Studies on the In Vitro Formation of Infectious DNA-Protein Aggregates from SV40 Components.** (Eng.) Christensen, M. (Dept. Biochemistry, Northwestern Univ. Medical Sch., Chicago, IL 60611) *Virology* 75(2): 433-441; 1976.

Purified complete and empty simian virus 40 (SV40) virions were disrupted in vitro at pH 10.6, and reassembly was attempted by three methods: (1) 18-hr dialysis at 4°C against Tris-NaCl-EDTA-2-mercaptoethanol, pH 8.0; (2) addition of 2 N HCl to immediately lower the pH to 8.0; and (3) addition of disrupted preparations directly to a neutral sucrose gradient and centrifugation. Although some reassociation occurred with all of these methods, treatment with HCl gave a population closer in S values (205S-252S) to the complete virion. The reassociated DNA-protein aggregates contained lower, varying ratios of DNA:protein than control virions. After reassociation, a portion of the DNA was sensitive to DNase treatment. This treatment led to a loss of the infectivity that had been found in the reassociated aggregates. Nucleic acid was not essential for physical reassociation, since aggregates reconstituted from disrupted complete virions had varying amounts of DNA, and further aggregates were readily assembled from disrupted empty shells. Disruption by the relatively mild conditions used indicates that the capsid is

held in its conformation in part by noncovalent linkage. The rapid reassociation as well as the absence of a low molecular weight protein after disruption suggest that the breakdown is not total. The nucleic acid is probably bound to the capsomeres by noncovalent linkages, since disruption led to the loss of a large amount of DNA. The rapid in vitro reconstitution of disrupted empty particles to protein aggregates similar to native empty shells strongly suggests that orientation of capsomeres into a tertiary conformation is fairly specific when unencumbered by the presence of DNA. Successful attempts were made to synthesize infectious aggregates in vitro using disrupted ¹⁴C-amino acid-labeled empty shells and the ³H-thymidine-labeled SV40 nucleoprotein complex obtained from infected cells 25 hr after infection. (14 refs.)

- 77-0257 **Initiation of DNA Synthesis and Uptake of T Antigen by Chick Erythrocyte Nuclei in Heterokaryons with SV40-Transformed Human Cells.** (Eng.) Dubbs, D. R. (Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX 77030) *Somatic Cell Genet* 3(1): 61-69; 1977.

The uptake of simian virus 40 (SV40) T antigen by chick erythrocyte (CE) nuclei after Sendai virus-induced fusion of the CE cells with SV40-transformed human skin cell (W98VaD) was compared with the initiation of DNA synthesis in the CE nuclei. Immunofluorescence showed that the CE nuclei rapidly became T-antigen-positive 16-28 hr after fusion; almost all of the CE nuclei were T-antigen-positive by 48 hr. The uptake of T antigen by the nuclei occurred at the same time, regardless of whether asynchronous or hydroxyurea-synchronized W98VaD cells were used. In contrast, DNA synthesis in the CE nuclei occurred as a function of time after the hydroxyurea block was removed from the host W98VaD cells. In particular, the CE nuclei of many heterokaryons synthesized DNA before they became T antigen-positive by immunofluorescence. It is suggested that the uptake of T antigen into the nuclei is not obligatory for the activation of nuclear DNA synthesis in CE cells. (27 refs.)

- 77-0258 **Application of a "Linked" Transcription Translation Cell Free System to the Direct Functional Mapping of a Mammalian Viral DNA.** (Eng.) Roberts, B. E. (Biology Dept., Massachusetts Inst. Technology, Cambridge, MA 02139) Danna, K. J.; Gorecki, M.; Mulligan, R. C.; Rich, A.; Rozenblatt, S. *INSERM* 47: 313-322; 1975.

Simian virus 40 (SV40) DNA was transcribed with a DNA dependent RNA polymerase from *Escherichia coli*, and the resultant RNA was transcribed by wheat germ extracts. The characteristics and requirements of this system were discussed. SV40 DNA form I directed the synthesis of discrete polypeptides up to 85,000 daltons. One of these proteins was identical to the authentic major virus capsid protein, VP1. In addition, one of the major cell-free products, a polypeptide of 60,000 daltons, was specifically immunoprecipitated with

SV40 T-antigen antiserum. VP1 was mapped in the late region of the DNA, to the left of the EcoRI cleavage site that is between 0.74 to 0 map units. The 60,000-daltons polypeptide was mapped in the early region, straddling map position 0.36. It is concluded that this SV40 system can be extended to the study of other viruses. With native reconstituted chromatin as templates, the system could also be used to elucidate the control of selective gene expression. (25 refs.)

- 77-0259 **Sequences in SV40 DNA Corresponding to the "Ends" of Cytoplasmic mRNA.** (Eng.) Dhar, R. Dept. Human Genetics, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT 06510) Subramanian, K. N.; Zain, B. S.; Levine, A.; Patch, C.; Weissman, S. M. *INSERM* 47: 25-31; 1975.

Oligonucleotide sequences in RNase digests of cytoplasmic polyadenylate-linked simian virus 40 (SV40) complementary RNA were compared with those of *Escherichia coli* RNA polymerase transcripts of segments of SV40 DNA. There was a stretch of nucleotides that showed considerable homology to the 3' end of certain cellular messenger RNA (mRNA) species at the 3' end of early mRNA. The 5' ends of early mRNA and the larger species of late mRNA overlapped by > 90 nucleotides. The 5' end of early mRNA was found to lie within the region of the origin of DNA replication. (28 refs.)

- 77-0260 **The Cell-Free Translation of Early and Late Classes of SV40 Messenger RNA.** (Eng.) Prives, C.; Aviv, H.; Gilboa, E.; Winocour, E.; Revel, M. In: *In Vitro Transcription and Translation of Viral Genomes. Proceedings of a Conference held in Paris-Grignon, 35-18 July 1975. INSERM, EMBO, DGRST. (Paris, France):* Vol. 47, pp. 305-312; 1975.

The three classes of SV40 mRNA extracted and purified from SV40 infected monkey cells (BS-C-1) directed the synthesis of polypeptide products when added to a cell-free translation system derived from wheat-germ extracts. The techniques used were gel electrophoresis and autoradiography. Late SV40 16S RNA directed the synthesis of a viral capsid protein, VP-1; the late 19S RNA directed synthesis of a peptide termed X-polypeptide. X-polypeptide appeared to be either a nonstructural viral protein or a precursor to a structural protein. Early SV40 19S mRNA directed the synthesis of four classes of polypeptides E₁-E₄ with molecular weights of approx 90,000, 44,000, 22,000 and 13,000 daltons. The E₁ polypeptide could be immunoprecipitated SV40 hamster antiserum but not hamster control serum. (16 refs.)

- 77-0261 **Aplastic Anaemia, Bone-Marrow Transplantation, and Polyoma and Other Virus Infections (Letter to Editor).** (Eng.) Henry, K. (Westminster Bone Marrow Transplantation Team, Westminster Children's Hosp., London SW1, England) Bird, R.; Watson, G.; Hugh-Jones,

K. *Lancet* 1(8013): 695-696; 1977.

The finding of virus infection in a child who received a bone marrow transplant from a sibling for aplastic anemia of unknown etiology is reported. The transplant was followed by episodes of graft-versus-host response and then by neurological symptoms. Before transplantation there had been no evidence of cytomegalovirus (CMV) infection, but there was afterward. In the urine, many of the desquamated epithelial cells showed nuclei that were largely replaced by polyoma virus particles of the BK strain. CMV was considered to be the cause of the child's fluctuating mental state. Polyoma virus in large numbers was also bound in the urine of a second child following bone-marrow transplantation. These cases raise some important questions, such as whether the BK infection was present before the bone-marrow transplant or before the numerous transfusions that the child received, and, if so, what is the relationship of aplastic anemia to polyoma virus. (2 refs.)

- 77-0262 **Polyoma Genome Transcription in Transformed Mouse Cells Growing in Culture and as Tumors in Syngeneic Mice.** (Eng.) Grady, L. J. (New York State Dept. Health, Div. Lab. Res., Empire State Plaza, Albany, NY 12201) North, A. B.; Campbell, W. P. *Int J Cancer* 19(2): 236-239; 1977.

Plaque-purified, small-plaque polyoma (PY) virus was grown on primary cultures of weanling mouse kidney cells using a multiplicity of infection of 0.1 plaque-forming unit per cell. Approx 25% of the E strand of viral DNA was transcribed in the transformed cells growing either in culture or as tumors in syngeneic mice. The extent of expression of the L strand of polyoma DNA was determined. Less than 3% of the L strand was transcribed in either PY AL/N cells or the concanavalin A (Con A)-selected revertant. On the other hand, tumor cells possessed RNA sequences complementary to approx 12% of the L strand. The viral RNA sequences complementary to the E strand were present at twice the concentration of those complementary to the L strand. When RNA from a Con A-selected revertant of the PY AL/N cells was employed, although complete saturation was not achieved, at least 16% of the E strand was expressed in the revertant. The results are consistent with the idea that not all of the E strand present in the cells is transcribed. (18 refs.)

- 77-0263 **Viral-Inhibiting Factor in Polyoma-Transformed Cells. I. Evidence from Cell Fusion.** (Eng.) Berebbi, M. (Unite 119 de l'I.N.S.E.R.M., 27, Bd Le Roure 13009 Marseille, France) Meyer, G.; Loche, M.; Cramer, R. *Virology* 76(1): 448-453; 1977.

Cells transformed by polyoma (Py) virus were examined for the presence of a factor inhibiting the replication of this virus. Mouse parental kidney cells were infected with Py virus and fused, either with normal or Py virus-transformed hamster

or mouse cells. The competence of the heterokaryons for inducing T antigen, cell DNA synthesis, and viral capsid formation was evaluated. The results indicated that the Py virus-transformed cells contain a factor that inhibits the production of mature Py virions. This factor cannot diffuse into the culture medium, and it requires direct cell contact for the inhibition. There was no inhibition of Py capsid protein synthesis when the Py-infected mouse kidney cells were not in contact with the other strains. It was not possible to detect an inhibition of cellular DNA synthesis induction or an inhibition of T antigen using immunofluorescent techniques. The viral-inhibiting factor seems to be specific for Py virus, but it may cross-react with simian virus 40 (SV40)-transformed cells. The situation of the viral-inhibiting factor seems analogous to that described for the transmission of morphogenetic signals. The signal of the viral-inhibiting factor might be transmitted to the nucleus of the permissive cells, thus inhibiting viral replication. (28 refs.)

- 77-0264 The Effects of Adrenal Glucocorticoid Hormones on Transformation by Polyoma Virus.** (Eng.) Rabinowitz, Z. (Dept. Biochemistry and Biophysics, Univ. California at San Francisco, San Francisco, CA 94143) Morhenn, V.; Mathews, M. B. *Virology* 75(2): 492-494; 1976.

The effect of glucocorticoids on polyoma virus transformation of nonpermissive cells was studied using normal fibroblasts from Golden Syrian hamsters. Primary hamster embryo fibroblast cultures were infected with polyoma virus and dexamethasone (dex) was added during the first 24 hr of cell-virus interaction. Macroscopically visible colonies were counted 3-4 wk after cloning in soft agar. Dex increased the frequency of transformation three- to fivefold. No colonies were observed in the absence of viral infection, either with or without the hormone. The stimulation of transformation was dose-dependent, and the response was apparent at low concentrations: 10^{-9} M gave a threefold increase. Max stimulation was observed at 10^{-8} M, and the response declined at higher concentrations. Cultures established from the transformed colonies were observed for 2-3 mo of in vitro propagation, during which time their transformed characteristics were preserved. This indicates that dex-promoted transformation is stable. Cortisol and progesterone, steroids known to interact with the steroid receptor, also stimulated transformation, but epicortisol, a biologically inactive epimer of cortisol, had no enhancing effect. These results suggest that the glucocorticoid receptor mediates transformation. (11 refs.)

- 77-0265 Isolation and Characterization of BK Virus-Transformed Hamster Cells.** (Eng.) Seehafer, J. (Dept. Biochemistry, Univ. Alberta, Edmonton, Alberta, Canada) Salmi, A.; Colter, J. S. *Virology* 77(1): 356-366; 1977.

Cultured baby hamster kidney (BHK) cells and hamster embryo fibroblasts (HE) were transformed by BK virus (BKV).

Twelve clones were isolated and characterized with respect to a number of biological properties. None of the cloned lines produced detectable BKV, and all gave uniformly negative results when stained for virion polypeptides by the indirect fluorescent antibody test. All lines of transformed HK cells grew in medium containing 0.5% fetal calf serum (FCS), a concentration that was inadequate for the growth of control HK cells. Only 2/6 transformed HE cell lines could grow in 0.5% FCS, although all grew in 1% FCS. Transformed cells had a higher saturation density and higher plating efficiencies than the corresponding untransformed cells. The former also produced colonies in soft agar and, when injected sc, progressively growing tumors in weanling hamsters. Sera from tumor-bearing animals contained antibodies to BKV T antigen, as shown by indirect immunofluorescence. The only significant change in these cells after a single passage in hamsters was an apparent tenfold increase in the ability of He-BK clone 1-1 cells to form colonies in soft agar. Infection by secondary cultures of HE cells with various input multiplicities of BKV showed that transformation is a multiplicity-dependent phenomenon and can be achieved with an input multiplicity as low as three plaque-forming units/cell. (16 refs.)

- 770266 Analysis of Polyoma Virus Induction in a Polyoma-Transformed Rat Cell Line by *in situ* Hybridization (Meeting Abstract).** (Eng.) Neer, A. (Dept. Biology, Technion-Israel Inst. Technology, Haifa, Israel) *Isr J Med Sci* 12(11): 1388; 1976. (no refs.)

- 77-0267 Neoplastic Potentials and Regulation of Uptake of Nutrients. I. A Glutamine Independent Variant of Polyoma BHK with a Very High Neoplastic Potential.** (Eng.) Gammon, M. T. (Dept. Medicine, Harvard Medical Sch., Boston, MA 02114) *J Cell Physiol* 89(4): 759-764; 1976.

A glutamine-independent variant of the polyoma BHK cell line (GIV) with a high neoplastic potential was evaluated. Differences in morphology were observed between the original polyoma transformed BHK (Py6), the nontransformed BHK, and the GIV lines. The Py6 cells demonstrated a typically disordered criss-cross pattern, and they had a rounded triangular or quadrangular appearance. The GIV cells showed a fibroblastic bipolar appearance more like that of the BHK cells, but not with the same organized pattern. The Py6 cells had a smaller cell vol than the BHK cells in both the subconfluent and confluent state. The av cell volume of the GIV cells was in an intermediate range and was greater in the subconfluent than in the confluent state. The growth rate of the GIV line on plastic dishes was less than that of the BHK and Py6 lines. Both BHK and Py6 cells were confluent by day 5 in culture. The BHK cells had significantly greater adhesion and detached less readily than the Py6 cells in the presence of 0.02% EDTA. However, the GIV cells showed detachment comparable to that of the parent Py6. In contrast to the BHK cells, the Py6 cells had an eight- to

fold increase in total lactic acid production by 4 days. However, the lactic acid liberation by GIV cells was low and was comparable to the BHK cells. GIV cells had a total galactosyltransferase activity that was 10 times greater than that of the BHK cells but comparable to that of the Py6 cells. In the presence of 25 µg/ml concanavalin A, GIV cells demonstrated greater agglutination than either BHK or Py6 cells. Inoculation of five hamsters with 10⁵ Py6 cells required 50 days for tumors to develop in all the animals. With the GIV cells, 5/5 hamsters showed tumors in 30 days. Furthermore, in the latter group, the tumors were larger and more numerous. GIV cells may be a useful tool for studying the mechanism of altered transport of nutrients by normal versus neoplastic cells. (19 refs.)

77-0268 **Viral Carcinogenesis.** (Eng.) Rosen, P. (Dept. Physics and Astronomy, Univ. Massachusetts, Amherst, MA 01002) *J Theor Biol* 64(2): 215-220; 1977.

A mathematical expression for transformation probability is derived using the assumption that the A gene of an oncogenic, temperature-sensitive mutant polyoma virus makes an A protein that binds to a regulator gene to cause transformation. The regulator gene is the operon controlling divisional proteins, its binding to A protein will prevent repressor protein from being synthesized, resulting in uncontrolled mitosis. The probability after long times is the concentration of the protein (CA) divided by the dissociation constant (KD). Calculations were compared to experimental data obtained by measuring transformation frequencies at 31.5 C as a function of virus concentration. Under proper temperature conditions, dissociation can occur. At 31.5 C, a reasonable estimate of KD is 10⁻⁷; at 38.5 C, transformation is very improbable. (refs.)

77-0269 **Evidence for Blocked 5'-Termini in Human Adenovirus DNA.** (Eng.) Carusi, E. A. (Dept. Biological Chemistry, Creighton Univ. Sch. Medicine, Omaha, NB 68178) *Virology* 76(1): 380-394; 1977.

DNA molecules from six human adenovirus serotypes, representative of three oncogenic classes, were investigated using enzymes specific for 5'- and 3'-termini in DNA. Results obtained with purified DNA indicated that the majority of the termini of all these DNAs are blocked. Depending upon the source of DNA, from 50%-80% of the 5' termini are inaccessible to polynucleotide kinase even after extensive alkaline phosphatase treatment. These termini are also resistant to 5'-terminal-specific λ exonuclease. The 5'-termini remain inaccessible to phosphorylation even after high-temperature phosphatase treatment or after phosphatase treatment of denatured, single-stranded DNA. However, about 40% of the blocked 5'-termini of adenovirus 2 DNA become accessible to phosphatase and polynucleotide kinase after prolonged treatment of the DNA with sodium hydroxide. To determine whether the DNA contained 3'-termini sensitive to exonu-

lease III, adeno 2 and 3 DNA were examined by sucrose gradient centrifugation after incubation with this enzyme. Over 90% of both types of DNA were attacked by the enzyme, indicating that all of the 3'-termini (but only 25%-30% of the 5'-termini) of these DNAs are accessible to specific exonuclease action. These findings suggest that a strongly bonded substituent rather than a peculiar DNA conformation accounts for the inaccessible 5'-termini. In all of the adenovirus serotypes examined, the nucleotide found at the 5'-termini of DNA molecules accessible to labeling was predominantly deoxycytidylate. There is some evidence that the 5'-blocking group may be a peptide or amino acid remnant of a protein cleaved during DNA purification, but several alternative structures accounting for blocked 5'-termini of linear DNA are also possible. (45 refs.)

77-0270 **Cell-Free Translation Products of Early RNA from Adenovirus Type 2-Infected KB Cells.** (Eng.) Eron, L. (Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014) Westphal, H. *INSERM* 47: 299-304; 1975.

Early RNA from adenovirus type 2 (Ad 2)-infected KB cells stimulated the synthesis of two polypeptides, Eα and Eβ, with molecular wts of 73,000 and 55,000, respectively, in a cell-free Krebs II ascites system. The in vitro translation products of late RNA from mock-infected cells included polypeptides comigrating on polyacrylamide gel electrophoresis with both Eα and Eβ and, in addition, a number of structural components of the virion. The peptide pattern of Eα was different from that of the respective mock counterpart, but identical patterns were observed for Eβ and mock Eβ. (23 refs.)

77-0271 **The Fate of Type 7 Adenovirions in Lysosomes of HeLa Cells.** (Eng.) Ogier, G. (Unite de Virologie Fondamentale et Appliquee, 1, Place du Professeur Joseph Renaut, 69008 Lyon, France) Chardonnet, Y.; Doerfler, W. *Virology* 77(1): 67-77; 1977.

When HeLa cells were infected with adenovirus 7 (Ad 7) and subsequently examined under the electron microscope, most of the virus was found to be engulfed by lysosomes. The percentage of intralysosomal virus was 50% after 10 min and 75%-80% between 1 and 2 hr. Viral particles remained morphologically intact inside the lysosomes up to 6 hr postinfection; their size, in particular, was unaltered. By 12 hr, however, intact viral particles could no longer be identified. The amount of infectious virus recovered from lysosomes at 2 hr postinfection remained unaltered after two neutralizations with specific antiserum; therefore, the infectious virus was actually inside the lysosomes. By 12 hr, no infectivity was recovered. The sensitivity of virion DNA to pancreatic DNase at 4 C increased during the first 2-hr absorption period, which suggests that some modification of the virion architecture occurred before transfer to the lysosomes. This sensitivity to DNase continued to increase with time after

infection. Intralysosomal Ad 7 particles underwent progressively degradation inside the lysosomes, and the degradation of the viral capsid was probably due to lysosomal enzymes. Intralysosomal particles were protected from the effect of acid DNase, since the virion DNA remained insensitive to this enzyme up to 6 hr postinfection. Intralysosomal Ad 7 DNA sedimented at 34S at 2 and 6 hr after the infection of HeLa cells. Comparable activities of free acid phosphatase were found in lysosomes isolated from uninfected and infected cells. In vitro, lysosomal acid DNase and pancreatic DNase degraded Ad 7 DNA at similar rates, but in vivo intralysosomal Ad 7 DNA was only partially sensitive to lysosomal DNase. (12 refs.)

77-0272 Identification of Early Proteins Induced by Highly Oncogenic Human Adenovirus 12 During Lytic Infection and in Hamster Tumors. (Eng.) Chinadurai, G. (Inst. Molecular Virology, Saint Louis Univ. Sch. Medicine, St. Louis, MO 63110) Jeng, Y.h.; Gilead, Z.; Green, M. *Biochem Biophys Commun* 74(3): 1199-1205; 1977.

At least seven early polypeptides (EP) induced by the infection of cultured human KB cells with the highly oncogenic human adenovirus 12 (Ad12) were resolved by electrophoresis on sodium dodecyl sulfate-polyacrylamide slab gels. Suspension cultures of KB cells were infected with Ad12 at a multiplicity of 100 plaque-forming units/cell. Ad12 infected and mock infected cells were incubated in 20 µg/ml of cytosine arabinoside (ara-C) (to prevent the expression of late viral genes) or 25 µg of cycloheximide (CH) (to enhance the synthesis of early messenger RNA relative to cell mRNA) for 8 hr. After incubation, these cells were washed with methionine-free growth medium containing 20 µg/ml ara-C and were labeled with ³⁵S-labeled methionine (20-250 µCi/mM) for 3 hr in isotonic (110 mM sodium chloride) or hypertonic (210 mM sodium chloride) medium. When infected cells were labeled in a hypertonic medium with CH pretreatment or pretreated with CH and labeled in either isotonic or hypertonic medium, six polypeptides were observed in Ad12 infected cells that were not detected in mock infected cells. The apparent molecular wt (MW) of these EP's (EP1, EP3-EP7) were 60,000, 15,000, 13,000, 12,500, 11,000, and 10,000, respectively. When the infected cells were labeled in an isotonic medium without CH pretreatment, only EP1 and reduced amounts of EP7 were seen. When induced tumor extracts of Ad12 infected cells pretreated with CH and labeled in hypertonic medium were immunoprecipitated with immunoglobulin G (100 µg) prepared from sera of hamsters bearing Ad12 induced tumors, the antiserum specifically precipitated EP1, EP6, and EP7 from labeled Ad12 infected cell extracts but not from mock infected cells. An additional polypeptide (EP2) with an apparent MW of 16,500, which could not be distinguished from a polypeptide of the same size in mock infected cell extracts, was also detected. The combination of a hypertonic medium and CH pretreatment enhanced the synthesis of low MW polypeptides (EP3-EP7) in Ad12 infected cells, whereas EP1 synthesis was reduced by CH pretreat-

ed cells. The polypeptides precipitated by Ad12 antiserum appear to be candidate transforming proteins based on the assumption that the transformed phenotype is maintained by the functioning of early viral coded proteins. (16 refs.)

77-0273 In Vitro Synthesis of Adenovirus Type 2 Early Proteins. (Eng.) Saborio, J. (Dept. Microbiology, Wallenberg Lab., Uppsala Univ., Uppsala, Sweden) Oberg, B.; Philipson, L. *INSERM* 47: 325-330; 1975.

An attempt was made to characterize the early virus-specific polypeptides of HeLa cells infected with adenovirus 2 (Ad2) using both in vivo and in vitro translation of mRNA extracted during the early phase of infection. In vivo studies indicated three virus-specific early polypeptides. Two polypeptides with estimated molecular wt of 19,000 and 10,000 correspond to the polypeptides E2, and E3; the third polypeptide, molecular wt 17,000, has not been reported. The 19,000 (E19K) and 17,000 (E17K) molecular wt proteins could be detected at 2 hr postinfection in the cytoplasm and nuclei; E10K was found only in the nuclear fraction. Increased labeling in the infected cells of polypeptides corresponding to a molecular wt of 70,000 was observed. Selective immunoprecipitation of two polypeptides with molecular wt of 70,000 and 45,000 was also achieved. These five polypeptides appeared to be primary translation products. At least all polypeptides but E45K were synthesized in vitro. These polypeptides were more or less conspicuous, depending on the preparation and concentration of RNA tested. Some other polypeptides, absent when mock-infected RNA was used, were conspicuous when RNA from infected cells treated with cycloheximide was used. Prominent bands were detected at 15K, 18K and in the region between 30K and 40K. They are believed to be virus specific, although no in vivo counterpart has been detected. (12 refs.)

77-0274 Epstein-Barr Virus Antibodies in the Blood Sera of Patients with Hodgkin's Disease. (Hun.) Czegledy, J. (Debreceni Orvostudományi Egyetem Mikrobiológiai Intézet, Debrecen, Hungary) Berenyi, E.; Gergely, L. *Magy Onkol* 20(3): 172-175; 1976.

Blood sera from 32 patients (16 men, 16 women) with Stage IA-IVB Hodgkin's disease and from immunologically normal nontumorous patients were investigated for antibodies to Epstein-Barr virus (EBV, intracellular virus capsid) antigen, cytomegalovirus antigen, and herpes simplex virus type 1 antigen by indirect immunofluorescence. Antibodies to EBV were found in all but one patient with Hodgkin's disease, and high titers (1:160 and over) were found in 22%. No antibodies were found in 25% of the control patients, and high titers were found in only 6%. The difference is statistically significant; a fivefold difference was found in the geometric means. The incidence of high antibody titers increased with the progression of the disease, being highest in patients with lymphocyte depletion, which may be due to the absence of T-cell clones with a suppressive effect, leading to the proliferation

of EBV-carrying cell clones. The Hodgkin's disease patients and the controls showed no difference concerning the cytomegalovirus and herpes simplex virus type 1 antibody titers. (17 refs.)

- 77-0275 **Expression and Regulation of Epstein-Barr Virus in Mammalian Cells.** (Eng.) Glaser, R. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 641-658; 1976.

The expression and regulation of Epstein-Barr virus (EBV) were studied in epithelial and fibroblast cells by making somatic cell hybrids of Burkitt tumor cells (HR-1 and Raji) using human (D98) or mouse (CLID) cells. Hybrid cells grown in HAT selective medium contained EBV DNA and EBV-associated nuclear antigen, but the virus genome was repressed. When D98/HR-1 cells were treated with iododeoxyuridine (IUdR), the EBV genome was induced, and after exposure to IUdR for 3 days, EBV early antigen was synthesized. Virus DNA synthesis was not observed and no virus capsid antigen (VCA) or membrane antigen (MA) could be detected. When the cells were grown in normal medium, after treatment with IUdR, virus DNA synthesis was observed and VCA and MA were detected by immunofluorescence. An enhancement in virus production and EBV-specific cytopathic effects was observed in both D98/HR-1 and D98/Raji cell lines that may be related to a host range effect on the replication of EBV. Both D98/HR-1 and CLID/Raji cells showed altered growth properties, suggesting that transformation characteristics associated with EBV genetic material may be capable of expression in nonlymphoblastoid cell types. The data also suggest that if an epithelial cell has the proper receptor, it can be infected with EBV, which has been shown with nasopharyngeal carcinoma epithelial tumor cells. (30 refs.)

- 77-0276 **Relationship Between Amount of Epstein-Barr Virus-Determined Nuclear Antigen per Cell and Number of EBV-DNA Copies per Cell.** (Eng.) Ernberg, I. (Dept. Tumour Biology, Karolinska Inst., S-10701 Stockholm 60, Sweden) Andersson-Anvret, M.; Klein, G.; Lundin, L.; Killander, D. *Nature* 266(17): 269-271; 1977.

The amount of Epstein-Barr virus-determined nuclear antigen (EBNA) per cell was measured by quantitative immunofluorimetry in different cell lines, in parallel with determining the av number of EBV-DNA copies, and a correlation between these two parameters was established. Eleven nonproducer lines were tested: Raji, Namalwa, Rael; RN2, RN17, RN21, 303L, 6410, F265, PESS, and AW-Ramos. There was a strong correlation between the number of EBV genome equivalents per cell and EBNA content. The Namalwa, 6410, and AW-Ramos lines had low numbers of EBV genome equivalents per cell, and they also had the lowest amount of EBNA per cell. Intermediate EBNA and EVB-DNA values were found for the 303L, F265, PESS, and Raji lines. The

three RN hybrids showed that the amount of EBNA per cell was amplified beyond the expected sum of the parents and was directly proportional to the amplified EBV genome copy number. The Rael cell line had a very low EBNA value per cell, but a somewhat higher EBV-DNA copy number than expected. It is suggested that the correlation found might be due to a viral gene-dosage effect. (25 refs.)

- 77-0277 **Efficiency of Transformation of Lymphocytes by Epstein-Barr Virus.** (Eng.) Henderson, E. (Dept. Pediatrics, Yale Univ. Sch. Medicine, New Haven, CT 06510) Miller, G.; Robinson, J.; Heston, L. *Virology* 76(1): 152-163; 1977.

Host cell and viral factors that influence the susceptibility of lymphocytes to transformation by Epstein-Barr virus (EBV) were explored. In most experiments, fresh human umbilical cord leukocytes (HUCL) were used, but blood was also obtained by venepuncture of adult humans and cotton-top marmosets. Transformation by the B95-8 strain of EBV followed one-hit kinetics. With a limiting dilution technique, 1/20 virus particles was transforming when assayed on HUCL. Mixed mononuclear WBC from adult human and marmoset blood were 100 and 1,000 times, respectively, less sensitive to transformation than HUCL. Pretreatment of cord blood WBC with phytohemagglutinin increased their transformability 50%. Lipopolysaccharide (LPS) from *Escherichia coli* increased transformation events by 300%-500%, apparently by mechanisms other than stimulation of cellular DNA synthesis. The number of cells transformed was determined by a transformed center assay using either autochthonous lymphocytes or human placental cells as feeders. At multiplicities of infection of 30-100 particles/cell, multiplicities that saturate nearly all the susceptible cells, 1/200-1/500 mixed mononuclear cells transformed. When the mixed population of cells was depleted of T lymphocytes, there was a fourfold increase in the number of transformed cells. Taking the plating efficiency of transformed cord blood WBC into consideration, it was calculated that at least 10% of virus-exposed cells establish permanent lines. When all variables are optimized, as many as 1/4 of virus-exposed B lymphocytes from HUCL may be found to be transformed. Whether these cells represent a special subpopulation of B lymphocytes with EBV receptors or whether all human B lymphocytes have the EBV receptor and only certain ones exhibit other physiologic characteristics that permit them to be transformed by the virus is not clear. (25 refs.)

- 77-0278 **A Case Control Study on Immunity to Two Epstein-Barr Virus-Associated Antigens, and to Herpes Simplex Virus and Adenovirus in a Population-Based Group of Patients with Hodgkin's Disease in Denmark, 1971-73.** (Eng.) Hesse, J. (Inst. Medical Microbiology, Univ. Copenhagen, Copenhagen, Denmark) Levine, P. H.; Ebbesen, P.; Connelly, R. R.; Mordhorst, C. H. *Int J Cancer* 19(1): 49-58; 1977.

Mean antibody titers to Epstein-Barr viral capsid antigen (EBV-CA) and to herpes simplex virus (HSV) in 185 untreated Hodgkin's disease (HD) patients were significantly higher than those in a matched control group: geometric mean titers to EBV-CA were 272.0 and 141.1 in HD and control groups, respectively, and 25.2 and 21.2 to HSV, respectively. No significant differences in mean titers to adenovirus common antigen were apparent. Significant case-control differences in EBV-CA titers were demonstrated only for the nodular sclerosis- and lymphocyte-predominant HD subgroups. After 1 yr of treatment, a significant rise in EBV-CA mean titer occurred: splenectomy promoted this elevation of titer. Neither the initial EBV-CA titers nor the subsequent elevated titers were related to prognosis. Although a relationship between EBV and HD does exist, elevated EBV titers are probably not of etiological significance in most HD patients. (38 refs.)

- 77-0279 Synthesis and Transport of Herpes Simplex Virus Proteins in Arginine-Deprived BSC-1 Cells.** (Eng.) Olshevsky, V. (Lab. Molecular Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel) *Isr J Med Sci* 12(11): 1298-1307; 1976.

BSC-1 cells infected with herpes simplex virus (HSV) type 1 (10 plaque-forming units/ml) were incubated at 37°C in media with and without arginine and labeled for different time intervals with 10 μ Ci/ml 35 S methionine starting at 3 hr postinfection. Labeled peptides present in the cytoplasm and nuclei were analyzed by polyacrylamide gel electrophoresis followed by autoradiography. Chase experiments using a complete medium showed that most viral structural proteins synthesized in the cytoplasm were selectively transported to the nucleus within 15 min of labeling, but some peptides required 20 to 40 min to reach detectable levels in the nuclei. In the presence of arginine, protein synthesis reached a max 7 to 10 hr after infection and then declined; when arginine was absent, synthesis decreased markedly. Only a few labeled proteins were transported slowly to the nucleus. Even after labeling for 60 min, some peptides could not be detected in the nucleus. The mechanism for this selective transport is not yet known. Because viral structural proteins remain in the cytoplasm and are rapidly degraded, the HSV DNA synthesized in the nucleus cannot be coated. This may be the reason why virions are not formed in the absence of arginine. (13 refs.)

- 77-0280 Type C Virus Activation in "Nontransformed" Mouse Cells by UV-Irradiated Herpes Simplex Virus.** (Eng.) Hampar, B. (Lab. DNA Tumor Viruses, NCI, NIH, Bethesda, MD 20014) Hatanaka, M.; Aulakh, G.; Derge, J. G.; Lee, L. *Virology* 76(2): 876-881; 1977.

Infection of nontransformed BLP mouse embryo cells with UV-irradiated herpes simplex virus (uv-HSV) resulted in the activation of an endogenous xenotropic C-type virus in each of 17 experiments. The levels of C-type virus activation de-

pended on both the multiplicities of infection (ranging from 10 to 1,947) and the periods of UV irradiation (6- to 20 min). Synthesis of C-type virus persisted for only a few days; most of the virus remained cell-associated. The highest levels of C-type virus synthesis occurred with low levels of UV irradiation (8-14 min), which eliminated cell killing of uv-HSV. (2 refs.)

- 77-0281 Increased Titres of Herpes Simplex Virus in Rauscher Leukosis-Infected Mice (Letter to Editor).** (Eng.) Barinsky, I. F. (D. I. Ivanovsky Inst. Virology, USSR Acad. Medical Sciences, 123098 Moscow, USSR) Tolmacheva, V. D.; Spynu, K. I. *Acta Virol* 20:443; 1976.

There have been conflicting reports on the interaction of herpes simplex virus (HSV) type 1, strain L₂, and oncornaviruses reproducing in the same cells. To study this problem, BALB/c mice were inoculated ip with Rauscher leukemia virus (RLV) suspensions and HSV was titrated in the same animals. Control titrations of HSV were done on mice not infected with RLV. Mice infected only with RLV served as additional controls. Virus titers obtained in RLV-HSV mice were higher by 2.25-3.0 log LD₅₀ than those in the controls. (2 refs.)

- 77-0282 Newcastle Disease Virus Protein Synthesis** (Eng.) Morrison, T. G. (Dept. Microbiology, Univ. Massachusetts Medical Sch., 55 Lake Ave., Worcester, MA 01605) Weiss, S.; Hightower, L.; Collins, B. S.; Bratt, M. A. *INSERM* 47: 281-289; 1975.

Cell-free protein synthesis was directed in extracts derived from Krebs II mouse ascites cells by using Newcastle disease virus (NDV) RNA isolated from chick embryo cells. The NDV 18S-22S RNA directed the synthesis of polypeptides with molecular wts of 30,000, 36,000, 40,000, 49,000, 56,000, and 66,000 daltons. The 66,000-dalton cell-free product corresponded to the viral HN glycoprotein of 74,000 daltons. Tryptic peptide analysis of the 56,000-dalton cell-free product revealed that it was identical to that obtained from the viral 66,000-dalton material, which was a mixture of the NDV nucleocapsid protein and the NDV F protein. The tryptic peptide patterns obtained from the authentic viral M protein and the 36,000- and 40,000-dalton polypeptides indicated no apparent relationship between them. The results of polyacrylamide gel electrophoresis of these cell-free reactions indicate that the NDV 35S RNA contains information for a polypeptide the size of the NDV L protein. (22 refs.)

- 77-0283 In Vitro Synthesis of RNA Containing 5' Terminal Structure 7mG (5') ppp(5') Apm...by Purified Wound Tumor Virus.** (Eng.) Rhodes, D. P. (Dept. Cell Biology, Roche Inst. Molecular Biology, Nutley, NJ 07110) Reddy, D. V.; MacLeod, R.; Black, L. M.; Banerjee,

A. K. *Virology* 76(2): 554-559; 1977.

A study is presented that demonstrates that purified wound tumor virus contains a methylase activity in addition to the previously reported virion-associated RNA polymerase. In the presence of the methyl donor S-adenosyl-L-methionine, the RNA transcripts corresponding to the 12 double-stranded genome RNA segments are methylated exclusively at their 5'-terminals. Elucidation of the 5'-terminal structure revealed that the methylation occurred in a blocked structure, $^3\text{mG}(5')\text{ppp}(5')\text{Apm}\dots$. This structure resembles the previously determined 5'-terminal structures of messenger RNAs synthesized in vitro by reovirus, vaccinia virus, cytoplasmic polyhedrosis virus, and vesicular stomatitis virus. (24 refs.)

77-0284 **Leukemia and the Reducing Property of Viruses.** (Eng.) Lohmann, W. (Institut für Biophysik der Universität, Strahlenzentrum, Leihgesterner Weg 17, D-6300 Giessen, W. Germany) *Radiat Environ Biophys* 3(4): 281-286; 1976.

Leukemia and the reducing property of viruses were investigated by determining the serum catalase activities of healthy children and adults and patients with acute leukemia. The activities of the healthy subjects were significantly higher than those of the patients and, in the former, the activity of the children was slightly less than that of the adults. Electron spin resonance spectra of blood samples were obtained. With the healthy persons, the spectrum exhibited a singlet approx 3.391 G broad and centered at approx 3,391 G. The patients always exhibited an additional peak located in the center of the singlet observed for healthy people. The height of this peak could be correlated to the WBC counts. Separation of the blood of the patients into several fractions demonstrated that the center peak was present in the spectra of WBC only; the spectra of RBC resembled those of normal sera. In healthy persons, the enriched WBC of blood samples used for transfusion exhibited a negligible center peak only. No signal was obtained in highly purified samples of granulocytes and lymphocytes. The addition of reduced glutathione to a fresh blood sample before separation resulted in the center peak when separated and purified samples of granulocytes and lymphocytes were studied. The addition of either potassium permanganate (3 mM) or oxidized glutathione (8 mM) to the leukemic blood immediately after drawing resulted in a spectrum that resembled the normal spectrum. In contrast, reduced glutathione (8 mM) added to normal blood immediately after drawing produced spectrum resembling that of a leukemia patient. The addition of oxidized glutathione (8 mM) to normal blood produced no change at all. The data suggest that, in the case of acute leukemia, the reducing substances (viruses?) might act in the peripheral blood. (16 refs.)

77-0285 **Isolation and Investigation of Biophysical Properties of Minimal Forms of Oncornaviruses** Type A and C. (Rus.) Zaitseva, O. V. (D. I. Ivanovskii Inst.

Virology USSR Acad. Medical Sciences, Moscow, USSR) Klitsunova, N. V.; Petukhova, M. B.; Glinskikh, N. P.; Bykovsky, A. F.; Ershov, F. I.; Zhdanov, V. M. *Vopr Virusol* (5): 587-591; 1976.

Differential centrifugation was used to concentrate and purify the minimal form of oncornavirus types A and C. They had heterogeneous distribution in sucrose density gradient and formed a peak in the 1.135 g/ml zone. Electron microscopy of the negatively stained preparations showed that the size of the minimal forms of oncornaviruses was 25 to 60 nanometers and the diameter of the nucleoids was 10 to 30 nanometers. (7 refs.)

77-0286 **Particles Resembling Oncornaviruses.** (Eng.) Bendheim, P. E. (Dept. Microbiology, Coll. Medicine, Univ. Arizona, Tucson, AZ 85724) *Arch Neurol* 34(2): 105-108; 1977.

A description is given of RNA-containing particles spontaneously released from thoracic cord meningioma tissue surgically removed from a 17-yr-old boy and maintained in cell culture at 37 C. The incorporation of tritiated uridine (50 $\mu\text{Ci/ml}$) into viral RNA synthesized during the experiments was determined by 15%-60% sucrose density gradient analysis. Untreated meningioma cells released labeled particles with a density similar to that of the Rous sarcoma virus (RSV) used as a density reference (about 1.15 g/ml). Treatment of cultures with 40-60 $\mu\text{g/ml}$ 5-bromodeoxyuridine did not enhance the production of RNA-containing virus. Particles isolated and purified on the sucrose gradients were disrupted by treatment with 0.5% sodium lauryl sulfate detergent in order to release the RNA for sedimentation analysis. The RNA species released had a sedimentation coefficient of 90S to 95S; RSV used as an external marker showed the 70S value. Results of both the density and sedimentation analyses indicated that oncornaviruslike particles were being produced by the meningioma cells. RNA-dependent DNA polymerase activity could not be detected, and possible reasons for this are discussed. The isolation of particles containing high molecular wt RNA does not implicate them etiologically. The ability of such particles to infect human cells remains to be proved. (18 refs.)

77-0287 **Biochemical and Electron Microscopical Evidence for the Presence of Oncorna Viruses in Spleen Tissue from Two Patients with Haematological Malignancies.** (Eng.) Warnaar, S. O. (Lab. Pathology, Univ. Leiden, The Netherlands) Te Velde, J.; Van Muijen, G.; Prins, F.; Van Der Loo, E. M.; Koopmans-Broekhuizen, N.; De Man, J. C. *Mol Biol Rep* 3(1): 1-8; 1976.

Ultrastructural and biochemical evidence for the presence of oncornaviruses in spleen tissue from patients with hematological malignancies is reported. The spleens of two patients, one weighing 5.5 kg from a 43-yr-old man suffering from non-

Hodgkin lymphoma and the second weighing 7 kg from a 28-yr-old woman suffering from an unusual variant of Ph + leukemia, were used. During purification of a reverse transcriptase from fresh tumor tissue, a clear association of this enzyme with a 1.16-g/cm³-density particle was found. After treating the particles with nonionic detergents on top of sucrose gradients, the enzyme was noted in two regions of the gradient. Approx 30% of the activity banded at a density of about 1.24 g/cm³, and the remaining activity was at the top of the gradient. No peak of enzyme activity was found at a density of 1.16 g/cm³. The activity profiles of the enzyme along the gradients were similar for both patients. To establish whether the enzyme was located in a viruslike particle that was converted to a viral core, a simultaneous detection assay was performed on an aliquot of the core material. The results demonstrated that newly synthesized DNA was associated with 70S or 35S RNA molecules. The material banding at a density of 1.16 g/cm³ contained sufficient viruslike particles for electron microscopic visualization. Particles resembling various stages of maturation of mammalian oncornaviruses were observed. The material contained very large numbers of particles of approx the same size as oncornaviruses with no or only very little internal organization. Considering the high reverse transcriptase activity and the numbers of viruslike particles, these particles may be very early precursors of human C type virus. (11 refs.)

- 77-0288 Oncornavirus-like Particles in Malignant Melanoma and Control Biopsies.** (Eng.) Parsons, P. G. (Queensland Inst. Medical Res., Herston Road, Brisbane, Australia) Klucis, E.; Goss, P. D.; Pope, J. H.; Little, J. H.; Davis, N. C. *Int J Cancer* 18(6): 757-763; 1976.

Oncornaviruslike particles in biopsies from 29 patients (18 men, 11 women) were investigated. Twenty-six of the samples were examined by the Spiegelman simultaneous assay, and 15 were positive. Of the 15 melanoma biopsies in which viruslike particles were detected, 5 were primary and 10 secondary tumors. The proportion of primary and secondary tumors with the particles was similar; 5/8 primary and 10/18 secondary tumors tested were positive. Nine of 13 secondary tumors in the lymph nodes and 1/4 in the skin were positive. There was no correlation between stage of the primary tumor and the presence or absence of viruslike particles. They were present in 11/19 biopsies from male patients and in 4/7 from female patients. The average age of the patients with particles was 50 yr, and that of the patients without particles was 58 yr. Lines of melanoma tumor cells were established from 3/15 biopsies containing viruslike particles and from 1/11 without detectable particles. Further information was obtained by velocity and sedimentation analysis, and 7/9 biopsy samples were positive. There was satisfactory evidence of viruslike particles in 21/31 of the biopsies. Two of 11 skin samples from patients with malignant melanomas (adjacent to the tumor) had evidence of particles, as did 1/4 tested by the simul-

taneous assay and 1/8 tested by velocity sedimentation analysis. None of three samples of normal adult skin demonstrated evidence of particles according to the simultaneous assay, but 2/5 were positive by velocity sedimentation. No evidence of particles was found in samples of five prepuces, one fetal muscle, and one umbilical cord. The exact nature of the particles remains to be defined. (15 refs.)

- 77-0289 Endogenous C-type Viral Expression in Primates.** (Eng.) Stephenson, J. R. (Lab. RNA Tumor Viruses, NCI, NIH, Bethesda, MD 20014) *Nature* 266: 469-472; 1977.

The antigenic divergence of structural proteins of prototype endogenous C-type virus isolates was investigated in primates. Antigens cross-reactive with *Papio cynocephalus* viral p30 were detectable in tissues of species representing each of five genera of Old World monkeys. The specificity of the antigenic reactivity was indicated by lack of competition in immunoassays for the p30 of other mammalian C-type viruses, including mouse and woolly monkey isolates. Species representing two primate genera, *Papio* and *Macaca*, exhibited significant differences in their tissue expression of viral p30. Macaque tissues had relatively high p30 levels, from 15 to > 100 nanograms/mg cellular protein. In most cases, baboon tissues had levels at least 20 times lower. The p30 antigens partially purified from liver tissues of *M. mulatta*, *Cynopithecus niger*, and *Cercopithecus neglectus* competed less efficiently than the p30 partially purified from *P. cynocephalus* liver tissue in the immunoassay for *P. cynocephalus* virus p30. Endogenous viral p30's of species representing different genera of Old World monkeys have undergone sufficient evolutionary change to make them immunologically distinguishable. (25 refs.)

- 77-0290 Control of Peptide Chain Initiation in Uninfected and Virus Infected Cells by Membrane Mediated Events.** (Eng.) Koch, G.; Oppermann, H.; Bilello, P.; Koch, F.; Nuss, D. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): Haematol Bluttransfus vol. 19, pp. 541-555; 1976.

The control of peptide chain initiation was investigated. HeLa cells were infected by poliovirus, type 1, strain Mahoney, or by vesicular stomatitis virus, serotype Indiana. To study the virus-induced increase in resistance of protein synthesis to hypertonic initiation block, the synthesis of individual cellular proteins in uninfected cells and of host and viral proteins early in the replication cycle in RNA and DNA virus-infected cells was determined. Cells were pulse-labeled under isotonic and hypertonic conditions, and cytoplasmic extracts were subsequently analyzed by polyacrylamide gel

electrophoresis. The exposure of virus-infected cells to appropriate hypertonic conditions amplified the inhibition of host messenger RNA (mRNA) translation, but viral mRNA translation was affected only slightly. The distribution of ^{35}S -methionine incorporation into MPC-11 (mouse plasmacytoma) polypeptides labeled under isotonic and hypertonic conditions was determined. There was a 3.5- to 4.0-fold increase in relative incorporation into the L chain under hypertonic conditions, compared to isotonic conditions. Likewise, there was an approx 1.5-fold increase in the relative incorporation into the H chain polypeptide. The percent of total ^{35}S -methionine incorporation, associated with the L chain, increased from 6.9% under isotonic conditions to 27.2% under hypertonic conditions. This value increased from 8.8% to 12.8% for the H protein. Initiation of protein synthesis in cell-free extracts was not affected by sucrose, ethanol, dimethyl sulfoxide, cytochalasin B, or L-1-tosylamido-2-phenylethyl chloromethyl ketone. When the overall rate of peptide chain initiation was decreased, host mRNA possessed less ability than viral mRNA to form mRNA-ribosome initiation complexes. It is proposed that control of protein synthesis on the translational level is amplified when the overall rate of complex formation between ribosomes and mRNA is indiscriminately lowered. When peptide chain initiation becomes rate-limiting, then all mRNA's with

high binding affinities to ribosomes are preferentially translated, and every mRNA species exhibits a characteristic ability to initiate translation. (35 refs.)

See also:

*(Rev.): 77-0045, 77-0046, 77-0047, 77-0048, 77-0049, 77-0050, 77-0051, 77-0052, 77-0053, 77-0054, 77-0055, 77-0056, 77-0057, 77-0058, 77-0059, 77-0061, 77-0063, 77-0069, 77-0089, 77-0091, 77-0092, 77-0093, 77-0094, 77-0097, 77-0107, 77-0114, 77-0115.

*(Chem.): 77-0181.

*(Phys.): 77-0194.

*(Immun.): 77-0291, 77-0299, 77-0300, 77-0303, 77-0307, 77-0322, 77-0338, 77-0339, 77-0342, 77-0343, 77-0347, 77-0349, 77-0350, 77-0352, 77-0354, 77-0355, 77-0356, 77-0361, 77-0362, 77-0363, 77-0366, 77-0369, 77-0370, 77-0373, 77-0374.

*(Path.): 77-0380, 77-0381, 77-0394, 77-0414, 77-0520.

*(Epid.-Biom.): 77-0538.

IMMUNOLOGY

77-0291 Leukaemias in BN/a and BN/b Mice After Prolonged Treatment with Antilymphocyte Globulin. (Eng.) Szkudlarek, J. (Dept. Tumour Immunology, Ludwik Hirsfeld Inst. Immunology and Experimental Therapy, Wroclaw, Poland) Radzikowski, C.; Czarnomska, A.; Dux, K.; Bartoszewicz, W. *Int J Cancer* 18(6): 829-834; 1976.

The leukemias in BN/b and BN/a mice following prolonged treatment with antilymphocyte globulin (ALG) were assessed. Injections of 10 mg immunoglobulin G/day were given to 3-wk-old mice every other day for the first week, then weekly until tumors developed or up to 1 yr. Of the total number of seven experimental groups, three showed an increase in the incidence of leukemia. The highest leukemia incidence (100%) was observed in mice treated for a short period with ALG D/7. BN/a mice succumbed to leukemia at the age of 50-75 days, and BN/b mice at the age of 50-60 days. ALG D/5, D/6, and D/7 given successively and ALG D/8 appeared to be less leukemogenic. Other ALG pools (D/9 and D/24) demonstrated no leukemogenic effect. Highly immunosuppressive ALG D/17 and D/18 + 19 also had no effect on leukemogenesis. Transplantability, as measured by av host survival time and number of regressions in syngeneic recipients inoculated ip with 10×10^6 of LBN/a-1 or LBN/a-2 cells and 25×10^6 of LBN/b-3 cells, was different in various passages of these leukemias. All mice inoculated sc with leukemic cells developed tumors that, after initial growth, regressed in 27/33 mice inoculated with LBN/a-1, in 20/33 mice inoculated with LBN/a-2, and in all 29 mice inoculated with LBN/b-3 cells. In all mice that rejected the primary graft, transplantation immunity was shown, as no tumor growth was detected after a second challenge with leukemic cells. In some cases, especially in groups of mice inoculated with LBN/a-2 leukemia cells, recipients that initially had rejected primary tumors developed generalized leukemia with involvement of spleen, lymph nodes, and thymus. Rabbit antiserum against soluble antigen from Rauscher leukemia virus gave a precipitation line identical to that of extracts from LBN/a-1, LBN/a-2, LBN/a-3, L-1210/V, and L-1210/S-1. Antisera prepared in the syngeneic system by immunization of BN/b mice with LBN/b-3 leukemia cells detected a common surface antigen in all three leukemias of BN mice and also in cells known to be infected with Gross virus. The only antigen detectable serologically on the surface of leukemic cells was related to infection with wild-type leukemia virus-Gross. (13 refs.)

77-0292 A Human IgA Myeloma Protein Interacting with Staphylococcal α -Toxin and Protein A. (Eng.) Dalen, A. (Gade Inst., Dept. Microbiology, Univ. Bergen, Bergen, Norway) Grov, A.; Matre, R.; Myking, O. L. *Clin Exp Immunol* 27(3): 421-424; 1977.

High antistaphylolysin activity (ASLA) was found in the serum of a 43-yr-old man with multiple myeloma. The ASLA was found in the monoclonal immunoglobulin A (IgA) protein. An interaction between staphylococcal α -toxin and IgA was evident on polyacrylamide gel electrophoresis. The IgA was thought to react with α -toxin through the Fc region of the molecule. An Fc-dependent interaction with protein A was demonstrated. The protein A nonreactive fraction was also strongly complexed with α_2 -macroglobulin, the reactive site of IgA probably being localized to the Fc region. These results strongly indicate an unusual Fc reactivity of the monoclonal IgA examined. (17 refs.)

77-0293 Idiotypic Immunoglobulin Structures on Blood Lymphocytes in Human Plasma Cell Myeloma. (Eng.) Holm, G. (Dept. Medicine, Serafimer Hosp., P. O. Box 12700, S-112 83 Stockholm, Sweden) Mellstedt, H.; Pettersson, D.; Biberfeld, P. *Immunol Rev* 34: 139-164; 1977.

Studies on human plasma cell myeloma are summarized. Cells belonging to a malignant clone were identified by immunofluorescence using antisera to idiotypic structures on monoclonal immunoglobulin. This technique permitted the identification of large numbers of nonclonal lymphocytic cells in the peripheral blood of patients with active disease. Such cells were demonstrated in four patients with IgG κ -myeloma and one with IgA κ -myeloma. A patient with IgG λ -myeloma had a simultaneous chronic lymphatic leukemia. In these patients idiotypic determinants located on the monoclonal immunoglobulins were demonstrated on peripheral blood lymphocytes and bone marrow plasma cells. Evidence is presented which indicates that the idiotypic structures on the surface of blood cells are synthesized by the cells which carry the idiotypic Ig. Idiotypic structures on blood lymphocytes and in plasmacytic cells are usually combined with γ -heavy chains in IgG-myelomas. Blood lymphocytes carrying μ and δ specificities are absent or rare during active disease. The results indicate that human plasma cell myeloma is a B-lymphocyte malignancy involving B-lymphocytes in different stages of differentiation. (45 refs.)

77-0294 Changes in Physiology of Enhanced SaI. (Eng.) Rubinstein, P. (New York Blood Center, 310 E. 67th St., New York, NY 10021) Suciu-Foca, N.; Streun, E. W.; Molinaro, A. P. *Transplant Proc* 9(1): 1171-1175; 1977.

Alterations in the physiology of enhanced sarcoma I (SaI) were examined. Groups of five B10.D2 mice each, all grafted with SaI, received one ip injection containing antibody at the time of grafting. Different concentrations of antibodies of each class were given, covering the range between 0.01 and

10 μ g of specific antibody. The minimal amounts required were, in molar terms, within a factor of two or three for all the classes, the least effective being the IgG2 classes. Sets of cultures in which 1, 2, 3, or 4×10^3 tumor cells had been plated were harvested at 41 and 63 days, after labeling with 3 H-proline or 3 H-thymidine. The results show that incorporation of label was approx a linear function of the number of cells plated, the incorporation of thymidine was almost identical for enhanced and nonenhanced cell lines, and a significant difference in proline incorporation existed between them. Tumor cells (1×10^4) were plated and incubated with effector lymphocytes in tumor:effector cell ratios of 1:1, 1:10, 1:25, 1:50, and 1:100. At all ratios, the nonenhanced cell line was more sensitive to killing by immune lymphocytes. Not only do antibodies stimulate tumor cell metabolism, they also render these cells less sensitive to attack by fully competent lymphocytes. (8 refs.)

- 77-0295 **Studies of Tumor-associated Immunoglobulins in Human Cancer.** (Fre.) Dorval, G. (Div. Immunologie Clinique, Hopital Royal Victoria, Montreal, Canada) Vanky, F.; Klein, E.; Wigzell, H. *Ann Immunol (Paris)* 128C(1/2): 111-112; 1977.

Immunoglobulin G (IgG) was detected by radioimmunoassay with protein A from *Staphylococcus aureus* on 14/16 sarcoma, carcinoma, and glioblastoma biopsy cultures. Unlike cells from normal tissues (skin, muscle, and lymph node), the tumor cells released IgG into the culture medium after 3 hr at 37 C. Iodoacetamide, 10^{-2} M (a metabolic inhibitor), prevented the release of IgG. Reincubation with nonautologous sera at 4 C induced rebinding of IgG by the uncoated cells. When autologous sera were used during the uncoating incubation, subsequent rebinding at 4 C from the same or other cancer sera was significantly decreased. The results suggest that IgG in the serum of cancer patients is capable of antigen modification of tumor cells. (1 refs.)

- 77-0296 **Immunoglobulin Synthesis in Hairy Cell Leukemia.** (Eng.) Golde, D. W. (Div. Hematology-Oncology, Dept. Medicine, UCLA Sch. Medicine, Los Angeles, CA 90024) Stevens, R. H.; Quan, S. G.; Saxon, A. *Br J Haematol* 35(3): 359-365; 1977.

Immunoglobulin (Ig) synthesis was investigated in the leukemic cells from two patients with hairy cell leukemia. Both patients (men 60 and 50 yr old, respectively) had clinically and morphologically well-defined disease, and their cells contained abundant tartrate-resistant acid phosphatase. One patient also had macroglobulinemia with immunoelectrophoretically documented monoclonal IgM in the serum. The B-lymphocyte nature of the hairy cells was indicated by fluorescent Ig staining, surface receptor properties, and electron microscopy. The kinetics of Ig synthesis were different in the cells from the two patients, as measured by equilibration time, intracellular degradation, and secretion. The neoplastic cells from the patient with macroglobulinemia synthe-

sized IgM both in vitro and in vivo. The cells from the other patient contained membrane and cytoplasmic Ig of only the IgG class, and they synthesized large quantities of IgG in vitro. Permanent cell lines established with cells from these patients grew as typical B-lymphoblastoid cultures and continued to produce tartrate-resistant acid phosphatase and Ig. These studies demonstrate the B-lymphocyte nature of the hairy cells in these patients and also provide evidence for a clonal origin of the leukemia. (24 refs.)

- 77-0297 **Immunological and Immunocytochemical Studies of the Inflammatory Infiltrating Cells of Cutaneous Tumors.** (Fre.) Viac, J. (Clinique Dermatologique, Hopital Ed. Herriot, 69374 Lyon Cedex 2, France) Schmitt, D.; Claudy, A.; Bustamante, R.; Perrot, H.; Thivolet, J. *Ann Immunol (Paris)* 128C(1/2): 109-110; 1977.

The absolute quantity of lymphocytes and the percentages undergoing T- and B-type rosette formation were measured in the inflammatory exudates of basal cell squamous cell carcinomas and malignant melanoma and by the delayed sensitivity reaction to tuberculin. The sensitivity reaction and the basal and squamous cell carcinoma exudates had a ratio of T to B lymphocytes of 5:1; equal numbers of T and B cells were present in the malignant melanoma exudates. Circulating T and B lymphocytes did not vary in their proportions from those of control subjects. The number of cells secreting the immunoglobulins (Ig) A, G, and M were measured in the exudates. IgA- and IgG-producing cells were comparatively numerous in the squamous and basal cell carcinoma exudates and low in the malignant melanoma samples. Again, similar alterations were not observed in the circulating lymphocytes. (no refs.)

- 77-0298 **Effect of Murine Tumor Sera on Adsorption of IgG-Sensitized Erythrocytes by Murine Sarcoma Tissue.** (Eng.) Targowski, S. P. (Dept. Microbiology, State Univ. New York Buffalo, Sch. Medicine, Buffalo, NY 14214) Abeyounis, C. J.; Milgrom, F. *Proc Soc Exp Biol Med* 154(3): 365-367; 1977.

The influence of sera from mice immunized with syngeneic tumor cells (methylcholanthrene-induced sarcomas MCSa-22 and MCSa-3) on the adsorption of sensitized RBC by tumor and spleen tissues was examined. The sera from 68 C3H/HeHa and 72 C57BL/6 mice immunized with the syngeneic tumors were tested for inhibition of hemadsorption. All sera tested gave inhibition. Immune serum inhibited hemadsorption up to a dilution of 1:40, but normal serum did not inhibit even at a dilution of 1:10. Inhibition was also obtained with immune serum heated at 56 C for 30 min. None of 72 sera from normal C3H/HeHa and C57BL/6 mice gave inhibition. The specificity of the hemadsorption inhibition with sera from mice immunized with syngeneic tumors was also determined. Immune sera from C57BL and C3H mice inhibited hemadsorption by both C57BL and C3H tumors. Similar results were obtained when normal spleen tissue from C57BL

and C3H mice were used in place of tumor tissue. Sera from tumor-bearing animals may contain immune complexes that block the Fc receptors of tumor and spleen cells indiscriminately. (7 refs.)

- 77-0299 Monoclonal Immunoglobulins, Cytomegalovirus Infection, and Malignant Blood Diseases.** (Fre.) Danon, F. (Laboratoire d'Immunochimie, UER Hematologie, INSERM U 108, Banque du Sangue et Laboratoire de Bacteriologie-Virologie, Hopital Saint-Louis, 75475 Paris Cedex 10, France) Bussel, A.; Perol, Y. *Ann Immunol (Paris)* 128C(1/2): 83-85; 1977.

The monoclonal immunoglobulins (Ig) G and M were detected in the sera of 7/29 patients under treatment with chemotherapy and blood transfusions for malignant blood disease. Cytomegalovirus (CMV) infection, confirmed by the presence of virus and/or an increase in anti-CMV antibodies in the blood, occurred in all seven patients, five simultaneously with increased IgG and/or IgM titers. The two male and five female patients ranged in age from 5-35 yr; three had acute myeloblastic leukemia (AML), three, acute lymphatic leukemia (ALL), and one, Hodgkin's disease. Except for one patient with AML, all were in remission at the time of CMV infection. They did not have evidence of proteinuria, plasmocyte infiltration, or, except for one with moderate hypo-Ig, abnormal polyclonal Ig. With one exception, in whom monoclonal Ig persisted for 4 yr after CMV infection, the five patients followed had no evidence of monoclonal gammopathy 6 mo after infection. (Two patients were lost to follow-up.) The immunological deficit may be attributed to the malignancy, the use of immunosuppressive drugs, and/or the viral infection. (3 refs.)

- 77-0300 Antibody-Dependent Cell-Mediated Cytotoxicity in the Moloney Sarcoma Virus System: Differential Activity of IgG and IgM with Different Subpopulations of Lymphocytes.** (Eng.) Lamon, E. W. (Birmingham Veterans Admin. Hosp., Dept. Birmingham, AL 35294) Shaw, M. W.; Goodson, S.; Lidin, B.; Walia, A. S.; Fuson, E. W. *J Exp Med* 145(2): 302-313; 1977.

Antibody-dependent cell-mediated cytotoxicity in the Moloney sarcoma virus (MSV) system was evaluated in terms of the differential ability of immunoglobulin G (IgG) and immunoglobulin M (IgM) from MSV regressor mice to induce cytotoxicity by lymphocytes from the lymph node, spleen, and thymus. Serum containing IgG and IgM was obtained from BALB/c mice 30 days after the injection of MSV (0.1 ml im). Lymphocytes were obtained from the spleens, lymph nodes, and thymuses of young adult CBA mice. Both IgM and IgG fractions of MSV regressor serum were able to induce specific cytotoxicity by lymph node cells. The end point titer for IgM against Ha2 target cells (established from an MSV-induced tumor of a CBA mouse) was 1:80, and the end point titer for IgG against Ha2 cells was 1:40. This cytotoxicity was specific for Ha2 target cells and was not seen

against Py3T3 cells (polyoma virus-transformed BALB/c 3T3 cells) or against D-56 cells (sarcoma positive, leukemia negative cells derived from 3T3 NIH Swiss embryo fibroblast cultures). To determine the relative efficiency of lymphoid cells from different organs as effector cells against antibody-coated target cells, the antibody fractions were placed on the target cells at a constant concentration (1:20) followed by graded numbers of lymphocytes from spleen, lymph node, or normal thymus. When IgM was used as the sensitizing antibody, as few as 2,500 lymph node cells produced a significant target cell reduction. Thymus required 5,000 cells and spleen 10,000 cells to produce a significant target cell reduction against the IgM-coated targets. When IgG was used as the sensitizing antibody, spleen and lymph node cells were equally efficient as effector cells (10,000 cells required); thymus cells, however, were not active against the IgG-coated tumor target cells. Cortisone treatment (2.5 mg cortisone acetate) of 6- to 8-wk-old CBA mouse donors of effector cells revealed that the cortisone-resistant subpopulation of thymocytes, 2 days after cortisone injection, exhibited an increased cytotoxicity against target cells treated with unfractionated antiserum and its IgM fraction. This subpopulation of thymocytes was also cytotoxic against IgG-coated target cells. At 12 days after cortisone injection, the repopulated thymus showed little change in activity against antibody-coated target cells in comparison to control thymus. (37 refs.)

- 77-0301 Comparison of Responses to Female and Male Tetraparental Mouse Chimeras to Lewis Lung Tumor.** (Eng.) Elbling, L. (Inst. Cancer Res., Univ. Vienna Borschkegasse 8a, A-1090, Vienna, Austria) Kurata, T.; Micksche, M. *IRCS Med Sci: Cancer* 4(12): 575; 1976.

The responses of male and female tetraparental mouse chimeras to Lewis lung tumor are compared. Tetraparental chimeras were produced by aggregation of B6D2F1 and SWA early embryos. A total of 20 animals per group (chimeras, B6D2F1, and SWA; both sexes) were inoculated with a lung tumor cell suspension (5×10^5) in the hind leg. The av tumor wt of the female chimeric mice was significantly greater than that of the B6D2F1 females on days 12 and 19. In the male groups, the tumors enlarged, but there was no significant difference between them. Chimeric males had a lower wt than chimeric females on day 12. In comparison, in B6D2F1 males the av tumor wt was greater than in B6D2F1 females on day 12 and 19. Both sexes of allogeneic SWA rejected the tumor. In chimeras, pulmonary metastases were markedly reduced in number in females, whereas they were extremely numerous in males. The number of lung metastases was comparable in female and male B6D2F1 animals. Androgens in B6D2F1 males may be more effective in stimulating primary tumor growth, but they may have no influence on metastatic spread. It is also possible that estrogens in females stimulate the immune system and thus lead to a higher resistance. A suppressed primary immune reaction in males may be an additional cause for initial enhanced tumor growth in syngeneic males. In sex-chimerism, the changed genetic and hormonal stimulation may be significant to primary tumor growth and

metastatic rate. It is concluded that, excluding sex differences, immunological mechanisms may be the actual cause of the enhanced growth of the transplantable tumor and of the changed metastatic spread in chimeras. (6 refs.)

- 77-0302 **Somatic Cell Hybrids Between Human Lymphoma Lines. III. Surface Markers.** (Eng.) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, S-10401 Stockholm 60, Sweden) Terasaki, P.; Billing, R.; Honig, R.; Jondal, M.; Rosen, A.; Zeuthen, J.; Clements, G. *Int J Cancer* 19(1): 66-76; 1977.

Genetically determined and/or differentiation-related surface markers were searched for in hybrids between two human lymphoma lines, Raji and Daudi (8A) and Raji and BJAB (83). The cultured lines were tested against a panel of 104 monospecific HL-A alloantisera covering 31 different specificities. HL-A, B-cell alloantigens, Fc and complement receptors, Epstein-Barr virus receptors, and B₂ microglobulin showed an autonomous (codominant) expression in the hybrid. In the hybrids, staining of activated complement and complement-consumption tests showed intermediate or partially suppressed expression. This result may be viewed in relation to the fact that these reactions do not merely depend on complement binding to the receptor, but also on subsequent activation and binding of the activated complement. Surface immunoglobulin showed a suppressive or intermediate pattern in both hybrids, but intracellular kappa chain production showed an amplification in the 83 hybrid. The β 2 microglobulin deficiency of the Daudi parent was corrected in the Raji/Daudi hybrid. Two new HL-A specificities, A10 and BW17, which were not present on the parental cell, appeared on this hybrid. Thus, the HL-A deficiency of the Daudi cell may be due to its lack of β 2 microglobulin. (33 refs.)

- 77-0303 **Immunization with p30 Enhances the Growth of a Rat Moloney Sarcoma.** (Eng.) Jones, J. M. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Kennel, S. J.; Feldman, J. D. *J Immunol* 118(1): 371-373; 1977.

BN rats were immunized with homogeneous preparations of p30, a core polypeptide, gp70, an envelope glycoprotein of type C RNA tumor viruses, and intact tumor cells to study their role in the growth and progression of challenge with a rat Moloney sarcoma (MST). Rats were challenged sc with 2×10^7 MST or 5×10^6 BC5 cells (a methylcholanthrene-induced sarcoma of BN rats) 7 days after immunization. In animals immunized with p30, MST progressed at an accelerated rate compared to the other groups. Tumor growth was minimal and tumors were eliminated in 8-10 days in rats immunized with MST. Tumor growth in animals immunized with gp70 was comparable to that in untreated controls. Six of eight animals immunized with p30 died by 38 days; all of the untreated controls and rats immunized with MST or gp70

were still alive. By 50 days, half the rats in the latter groups and all those in the p30 immune group had died. Immunization with MST or p30 did not influence the growth of BC5, which indicates specificity of protection and enhancement. Tumors in rats injected with anti-p30 antiserum attained a larger size than those in rats injected with normal BN serum. When mixed with MST, spleen cells of p30-immunized rats failed to enhance tumor growth compared to normal spleen cells. Before tumor challenge, sera of rats immunized with p30 contained antibody to p30 but not to gp70 and vice versa for sera of animals immunized with gp70. Animals immunized with MST exhibited antibody to p30 and gp70. The presence of serum antibody to p30 did not always lead to enhancement, since animals immunized with MST also produced anti-p30 but were resistant to tumor challenge. These animals also produced cytotoxic antibody, and this along with factors such as cellular immunity might have been sufficient to overcome any influence of anti-p30 antibody. (15 refs.)

- 77-0304 **Production of Factors with Immunosuppressive Activity by a Murine Lymphoblastoid Tumor Cell Line.** (Eng.) Mansfield, J. M. (Dept. Microbiology Immunology, Sch. Medicine, Univ. Louisville, Louisville, KY 40201) Shannon, W. M.; Yen, S. E.; Wallace, J. H. *Proc Soc Exp Biol Med* 154(3): 341-345; 1977.

The release of a lymphokineline factor from an isolated clone of L1210 cells was evaluated. Both frozen and lyophilized-reconstituted L1210/A3 culture fluids (SF) exhibited macrophage migration inhibitory factor (MIF)-like activity in vitro with normal syngeneic, allogeneic, or xenogeneic peritoneal macrophage cells. Lysates of L1210/A3 cells did not possess significant MIF-like activity. The activity associated with L1210/A3-SF was not due to cytotoxicity, since excessively high concentrations (5,000 μ g/ml) failed to alter the viability of peritoneal macrophages during a 48-hr incubation period. The MIF-like activity was demonstrable with SF preparations containing as little as 25 μ g protein/ml. The injection of SF in amounts of ≥ 50 μ g up to 3 days prior to or on the same day as sheep RBC injection resulted in a subsequent suppression of splenic plaque-forming cell responses to sheep RBC. Injection of SF iv or ip resulted in immunosuppression. The addition of SF to spleen cell cultures undergoing a primary in vitro antibody response to sheep RBC resulted in suppression of the resultant day plaque-forming cell responses. The secretion of an immunosuppressive factor by L1210 cells may be an example of tumor-cell-associated mechanisms that alter host immune system function. (33 refs.)

- 77-0305 **Studies on NZB Mice. III. Failure of Growth of Isogeneic Tumors Transplanted to Old NAB Mice.** (Spa.) Rodriguez Paradisi, E. (Istit. "Angel Roffo", Secc. Immunogenetica. Av. San Martin 5481, Buenos Aires, Argentina) De Bonaparte, Y. P.; D'Elia, I.; Klein, D. *Sangre*

21(4): 805-813; 1976.

The transplantation of isogeneic tumors into NZB mice was investigated. Thymus and thymus-derived cells accelerated growth of transplanted syngeneic tumors. Thymectomy had opposite results: NZB mice developed an ageing-related loss of a variety of thymus-dependent functions. NZB mice of a wide range of ages were transplanted with two types of neoplasms: one allogeneic, a C3H-methylcholanthrene-induced (MC) and two syngeneic tumors: a reticulum cell neoplasm type A (RSA) and an osteosarcoma (OS). Old NZB mice (310 to 629 days) transplanted with allogeneic tumor (MC) developed large tumor masses (up to 9 x 8 mm). Almost all (84.6%) tumor grafts were successful. Two old animals died from their tumors. Young NZB (70 to 87 days old) had barely palpable tumors in only 25% of the successful tumor grafts. After 30 days, all the young animals had rejected their tumors; only one diminishing tumor mass (2 x 3 mm) remained in one old animal. Statistically significant delay of tumor appearance and diminution of the rate of takes were observed in 11- to 17-mo-old-NZB mice transplanted with RSA as compared to younger mice of ages ranging from new-born (12 to 14 days old) to 8 mo (230 to 256 day old). When young and old NZB mice were transplanted with OS, a greater av of final local tumor wt was found in the 37- to 44-day-old group in comparison with an old NZB group, 318 to 531 days old. This clearcut difference between young and old animals was not repeated when additional groups of young (75- to 98-day-old) and old (362- to 541-day-old) NZB mice were assayed. Moreover groups of young (113- to 130-day-old) and old (449- to 650-day-old) NZB mice, which previously had rejected an allogeneic MC tumor, developed similar final local tumor wt when submitted to a new OS grafting. (24 refs.)

- 77-0306 A Study of Immunological Effects of Intrathymic Injection of Carcinogen in Adult Albino Rats.** (Eng.) Kameswaran, L. (Dept. Pharmacology, Madras Medical Coll., Madras, India) Kanakambal, K. *Indian J Med Res* 64(9): 1335-1341; 1976.

The immunological effects of the intrathymic injection of 9,10-dimethyl-1,2-benzanthracene (DMBA; 1 µg in 0.1 ml sesame oil) were investigated. The wt of the thymus demonstrated a significant increase during the 6 mo of observation. Microscopic study suggested proliferative changes (germinal follicle formation) and increased cortical activity in the thymus after 1 mo. Pleomorphic changes suggesting increased cortical activity were noted in the lymph nodes, and the spleen showed congestion. There was an increase in the peripheral total WBC count and absolute lymphocyte count that reached a max 3 mo after the injection of DMBA. A significant increase in total serum protein with an elevation in gamma globulin was a delayed response and was seen at the time of max lymphocytosis. Mast cells in the thymus increased and demonstrated persistent degranulation. They also encroached into the parenchyma; the controls, however, showed a subcapsular distribution. These changes in the

thymus were found to be associated with similar changes at distant tissue sites, such as sc tissue, the mesentery, skin, and pleura. The histamine content of tissues such as the dorsal skin demonstrated a persistently lower level than that of controls. It is suggested that, in response to the injected DMBA the thymus acted through both cellular and humoral mechanisms. (16 refs.)

- 77-0307 Reversal of SV40 Tumor-Mediated Suppression of Spleen Cell Cytotoxicity by Antibody.** (Eng.) Prather, S. O. (Dept. Microbiology, Specialized Cancer Research Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033) Lausch, R. N. *J Immunol* 118(1): 203-210; 1977.

The reversal of simian virus 40 (SV40) tumor-mediated suppression of spleen cell cytotoxicity by antibody was investigated by the visual microcytotoxicity test. Hamsters were inoculated with 10⁴ syngeneic PARA-7 tumor cells [derived from a clone of hamster embryo fibroblasts transformed in vitro by the PARA (defective SV40)-adenovirus 7 hybrid virus]. After incubation in vitro for 2.5 or 24 hr, spleen cell pools from each group were tested for cytotoxicity against PARA-7 target cells. Cells from animals bearing isografts for 7, 10, and 14 days were increasingly cytotoxic for the tumor cells, and the degrees of killing after the short or long incubation period were comparable. However, the incubation period did affect the cytotoxic capability of spleen cells from donors with tumors larger than 1 cm. Spleen cells incubated for 2.5 hr exhibited reduced (day 21) or no (days 32 and 42) cytotoxicity. In contrast, spleen cells incubated for 24 hr exhibited nearly max responsiveness. Following 24 hr of incubation, supernatants overlying spleen cells from tumor-bearing hosts contained a factor that blocked the cytotoxicity of SV40-sensitized spleen cells at the PARA-7 target cell level. The treatment of inactive spleen cells with anti-hamster γ globulin in the presence of complement prevented the formation and activation of blocking factor. Spleen cells from hamsters bearing small PARA-7 tumors were consistently cytotoxic for PARA-7 target cells in the microcytotoxicity assay. In contrast, spleen cells from animals with large tumors were not cytotoxic on immediate testing but were activated by overnight in vitro incubation. The data suggest that tumor antigen binds to killer cells with a consequent abrogation of cytotoxicity; this may be a significant factor mediating survival of the immunogenic PARA-7 tumor cells in vivo. (35 refs.)

- 77-0308 Phenotypic Alteration of Isoenzyme Profiles of Alkaline Phosphatase in HeLa TCRC-1 Cells Growing in Immunosuppressed Rats.** (Eng.) Singer, R. M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 177-184; 1976.

The alteration in the phenotypic expression of the isoenzymes of alkaline phosphatase by growth of human cells in animal hosts was observed for the first time. HeLa TCRC-1, a cell

ine monophenotypic for high levels of the Regan isoenzyme, was grown in neonatal immunosuppressed rats as a solid subcutaneous nodule. Acrylamide gel electrophoresis revealed a decrease in the Regan isoenzyme with a simultaneous appearance and increase in new fast-moving isoenzyme bands. After 30 days of growth in vivo, no Regan isoenzyme was visible. A single fast-moving isoenzyme band was dominant and was identified as the onco-amnionic (FL) isoenzyme first characterized in the FL amnion cell line and later in a hepatoma patient. The cells regained their original Regan phenotype 1-2 wk after transfer of the tumors back to culture. The growth of human cancer cells in immunosuppressed animals may provide a model system of tumor growth that would simulate growth phenomena in the intact human organism more closely than would in vitro techniques. (17 refs.)

77-0309 Immunosuppression of T Lymphocyte Function by Fractionated Serum from Tumor-Bearing Mice. (Eng.) McMaster, R. (Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia, Canada V6T 1W5) Buhler, K.; Whitney, R.; Levy, J. G. *J Immunol* 118(1): 218-222; 1977.

The immunosuppression of T lymphocyte function by fractionated serum from tumor-bearing (3-methylcholanthrene-induced rhabdomyosarcoma) and normal DBA/2J mice was evaluated. Serum from tumor-bearing and normal DBA/2J mice was fractionated on Sephadex G-150, precipitated, reconstituted, and dialyzed. At higher concentrations, the serum fraction from normal mice was somewhat inhibitory; at all concentrations, the fractionated tumor serum was more inhibitory. The fractionated tumor serum inhibited the generation of plaque-forming cells when added during the first 2 days of incubation. There was no inhibition when it was added after day 2. The generation of syngeneic cytotoxic lymphocytes was inhibited by fractionated serum from tumor-bearing mice. Spleen cells were taken from mice that had been injected 14 days earlier with 10^4 P815 cells, and cultured with mitomycin C-treated P815 cells. Fractionated serum was added to cultures on consecutive days to a final concentration of $600\mu\text{g/ml}$. Cytotoxic activity was measured on day 5. As with allogeneic cytotoxic lymphocytes, the response was inhibited by fractionated serum from tumor-bearing mice if present during the first 2 days of culture. Serum fractions added after this were noninhibitory. The serum factor appears to inhibit the generation of specific T cell function during the proliferative stage of development but has no effect on the differentiation stage leading to either cytotoxic lymphocytes or antibody-producing cells. (23 refs.)

77-0310 Immunosuppressive Properties of Human Alpha-Fetoprotein and Human Cord Plasma Albumin. (Eng.) Goeken, N. E.; Thompson, J. S. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 307-315; 1976.

α -Fetoprotein (AFP) and albumin (HCA) were purified from

human cord serum by immunoabsorbant chromatography. Both proteins exhibited immunosuppressive activity when tested in phytohemagglutinin-stimulated and human mixed lymphocyte cultures (MLC). Dose response curves were similar, each demonstrating 50% suppression of the MLC between 100 and $200\mu\text{g/ml}$. However, immunoabsorbant-isolated, adult albumin and commercial albumin produced no suppression over the same dose range, suggesting that the activity of albumin is dependent on the source from which it is isolated. This could be attributed to the presence of low molecular wt suppressive substances. The immunosuppressive properties of AFP and HCA may be a reflection of their ability to bind other active moieties rather than intrinsic characteristics of the proteins themselves. AFP may be a carrier for immunosuppressive substances. (20 refs.)

77-0311 Cellular Aspects of Alpha-Fetoprotein Synthesis. (Eng.) Abelev, G. I. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 191-202; 1976.

Further understanding of the cellular synthesis of α -fetoprotein (AFP) requires identification of the cells producing AFP. Immunofluorescent studies have demonstrated that AFP-containing cells include yolk sac endoderm, most fetal hepatocytes, some but not all newborn hepatocytes (in the rat), yolk sac structures or embryonal liverlike tissue, teratocarcinomas, variable numbers of hepatoma cells, and, during hepatocarcinogenesis, carcinoma cells. A new micromethod for picogram quantities of antigens is briefly described. The antigen is first concentrated by electrophoresis, immunodiffusion in medium containing monospecific antiserum, and visualization by autoradiography. This method has been found useful for detecting AFP from microcolonies of human hepatocytes. (28 refs.)

77-0312 Effect of AFP on Immune Phenomena in Rats and Mice. (Eng.) Sheppard, H. W.; Poler, S. M.; Trefts, P.; Sell, S. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 317-327; 1976.

The effect of normal sera, amniotic fluid, sera from tumor-bearing rats and α -fetoprotein (AFP) on immune reactions of rats and mice was studied. AFP was partially purified by affinity chromatography. Preliminary results indicated that whereas some reactions are inhibited by AFP, other in vitro systems were only weakly inhibited, unaffected or even enhanced by the addition of AFP. In the rat, the mitogenic response of lymph node cells to phytohemagglutinin (PHA) was slightly inhibited by AFP from amniotic fluid (Am-AFP) but not by AFP from tumor sera (Tu-AFP). Body fluids with 10,000-fold differences in AFP concentration A response were not inhibited. In mice there was no difference between the effect of Am-AFP and Tu-AFP on any of the in vitro reactions studied. Mouse AFP inhibited the lipopolysaccha-

ride (LPS) mitogenic response but not the response to concanavalin A. Very high concentrations of AFP only partially inhibited in vitro plaque forming cell (PFC) responses to sheep RBC and the secondary in vitro PFC response to keyhole limpet hemocyanin conjugated to trinitrophenol. The induction of cytotoxic effector cells directed against P 815 mastocytoma cells was ninefold higher in the presence of AFP. AFP alone was mitogenic for murine lymphoid cells. AFP may stimulate a subpopulation of lymphoid cells to act as suppressors for some B cell mediated reactions. (31 refs.)

- 77-0313 Two New Rat Hepatoma Cell Lines for Studying the Unbalanced Blocked Ontogeny Hypothesis.** (Eng.) Becker, J. E.; de Nechaud, B.; Potter, V. R. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 259-270; 1976.

Two epithelial cell lines (McA-RH8994 and McA-RH7777) derived from Morris hepatomas 8994 and 7777 were established in culture. Both lines, like the parent tumors, produced α -fetoprotein (AFP). The peak of AFP secretion into culture medium occurred during the logarithmic phase of the growth curve. Both lines are capable of growth in serum-free medium although at a reduced rate when compared to serum-containing medium. In serum-free medium, addition of dexamethasone (DEX) reduced cell multiplication and increased AFP production in McA-RH8994; DEX reduced cell multiplication and increased AFP production in McA-RH7777. McA-RH7777 produced AFP and albumin (Alb) at 600:1. McA-RH8994 started to secrete α -M-fetoprotein either after addition of glucocorticoids or at the end of the log phase of growth. These cell lines, both producing "transitory cell antigen" but having different responses to DEX, can be used to study the "unbalanced blocked ontogeny" concept. (46 refs.)

- 77-0314 Alpha-Fetoprotein from Two Variants of the Morris Hepatoma 7777: Effects on the Rat Mixed Lymphocyte Reaction.** (Eng.) Parmely, M. J. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 297-305; 1976.

Two variants of the Morris hepatoma 7777 were found; both secrete large amounts of α -fetoprotein (AFP), but the variants differ immunologically. These two variants of the Morris hepatoma 7777 were propagated and used to study immunoregulation in tumor-bearing Buffalo strain female rats. AFP-rich fractions isolated from the "Iowa" variant of the tumor showed mixed lymphocyte reaction (MLR) suppression, while similar fractions from the "San Diego" variant did not interfere with lymphoproliferation. When these fractions were further chromatographed by gel filtration, MLR-suppressive activity dissociated from the AFP and was found instead with apparently normal serum α -globulins of higher molecular wt. AFP that was further purified by immunoabsorption was indistinguishable from albumin in its effect on the MLR. High molecular wt α -globulin fractions from nor-

mal Buffalo rat serum also inhibited lymphocyte proliferation. The factors from hepatoma-bearing rats responsible for MLR suppression may not be oncofetal antigens but simply quantitative alterations in normal α -globulin components. (11 refs.)

- 77-0315 Onco-Fetal Antigens in Chromatin of Malignant Cells.** (Eng.) Chiu, J. F.; Chytil, F.; Hnilica, L. S. In: *Onco-Fetal Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 271-280; 1976.

Tissue-specific antibodies were elicited in rabbits against complexes of DNA with a group of chromosomal, nonhistone proteins (NP-DNA complexes). The localization of the antigens was studied by the horseradish peroxidase bridge technique. The antigens were localized in the nuclei and nucleoli with essentially no accumulation in the cytoplasm. Administration of 3'-methyl-4-dimethylaminoazobenzene to Fischer rats changed the NP-DNA immunospecificity of liver chromatin to a new type of specificity common to many experimental malignancies. Tumor-specific NP-DNA complexes were also detected in chromatin of embryonic tissues and in regenerating rat liver (24-48 hr after hepatectomy). Immunoabsorption experiments indicate the presence of at least two kinds of specific antibodies in the antisera against Novikoff hepatoma dehistonized chromatin. One was oriented against antigens common to highly proliferative tissues and the other was oriented against antigens specific for malignant tumors. The in vitro transcription of isolated chromatins was significantly inhibited by the addition of homologous antisera to the assay mixtures. These findings suggest that the composition of nuclear nonhistone proteins is associated with cell differentiation. (26 refs.)

- 77-0316 Recent Results Concerning the Beta Onco-Fetal Antigen (BOFA).** (Eng.) Fritsche, R.; Carrel, S.; Ritter, U.; Mach, J. P. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976*. International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 523-527; 1976.

Further characterization of the β oncofetal antigen (BOFA) is presented. BOFA was first purified from a hepatic metastasis of a colon carcinoma by Sephadex G-200 filtration and elution with 3M NaSCN. Twenty-five μ g of purified BOFA were incubated in sodium dodecylsulfate gel and analyzed: a major protein band and two faint additional bands of higher molecular wt were detected. The major band had a molecular wt of 75,000 to 80,000 daltons. Moderate staining with PAS indicated that BOFA contains a small amount of carbohydrate. Immunofluorescence was examined with anti-BOFA antiserum and colon carcinoma. Fluorescence was detected mostly at the periphery of the tumor cells in a patchy distribution. In tumor cells fixed with acetone or ethanol, the

fluorescence also appeared at the periphery of the cells, but the presence of BOFA in the cytoplasm could not be clearly demonstrated. (12 refs.)

77-0317 **Marker Antigens and Immunization with Heterologous AFP in Germinal Tumors of the Testis.** (Eng.) Wahren, B.; Esposti, P.; Gadler, H.; Alpert, E. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 147-154; 1976.

Three antigens associated with fetal tissues and malignancy were found in tumor cells and serum of patients (43 with teratomas, five with seminoma of the testis). These were α -fetoprotein (AFP), carcinoembryonic antigen, and ferritin. Indirect immunofluorescence on cell smears demonstrated a mainly cytoplasmic localization of all three antigens. Each of the antigens occurred with a different frequency in different cell populations, indicating that different subpopulations exist in a given tumor. Raised serum levels of AFP and/or ferritin were related to the presence of tumor and to the dissemination of the disease. Two patients with advanced tumor and raised serum AFP were immunized with heterologous AFP. These patients formed antibody to the heterologous rabbit AFP injected, and their endogenous serum AFP decreased. (12 refs.)

77-0318 **Immunization of Mice Against Autologous Alpha-Fetoprotein (AFP)--Reduction of Serum AFP During Tumorigenesis but Lack of Effect on Incidence of Transplanted Hepatomas.** (Eng.) Ruoslahti, E.; Engvall, E.; Jalanko, H.; Pihko, H. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 349-353; 1976.

Immunization of rabbits, monkeys, rats, or mice with heterologous α -fetoprotein (AFP) elicited antibodies, which also reacted with the animals' own AFP. These homologous anti-AFP antibodies were of low avidity, but did eliminate the normal serum AFP. Homologous anti-AFP antibodies reduced the amount of AFP present in serum during tumorigenesis. They failed to protect C57L mice against transplantation with an AFP-producing hepatoma. Recent results have shown sequence homology and immunology cross-reactivity between AFP and albumin. The use of albumin as the control immunization for tumor transplantation may be invalid. The results suggest that AFP is a fetal counterpart of albumin. (12 refs.)

77-0319 **Partial Purification and Immunochemical Characterization of the Carcinoembryonic Antigen in Xenografted GW-39 Human Colonic Tumors.** (Eng.) Munjal, D.; Goldenberg, D. M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 621-624; 1976.

Carcinoembryonic antigen (CEA) was extracted with perchloric acid from GW-39 human colonic tumors xenografted in hamsters. The extract was further purified by passing successively through Bio Gel A-15m, DE 52, and Bio Gel A-1.5m columns. CEA yield from this procedure was 10-15 μ g per g of GW-39 tumor. GW-39 tumor CEA and radiolabeled CEA were eluted together, indicating a similar size range. The molecular wt was $200,000 \pm 20,000$. When tested against anti-CEA antiserum and pure CEA from a colonic cancer metastasis, GW-39 CEA showed immunological identity in gel diffusion plates and by antibody-inhibition curves in radioimmunoassay. A single band was obtained in polyacrylamide disc gel electrophoresis and immunoelectrophoresis, indicating that the preparation was homogeneous. Thus CEA from GW-39 appears immunologically identical to the CEA from a reference metastatic, colonic cancer CEA. These and other results indicate that CEA size and yield can vary from tumor to tumor. (13 refs.)

77-0320 **Natural Anti-tumor Serum Reactivity in BALB/c Mice. I. Characterization and Interference with Tumor Growth.** (Eng.) Menard, S. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy) Colnaghi, M. I.; Della Porta, G. *Int J Cancer* 19(2): 267-274; 1977.

A rabbit complement-dependent cytotoxicity test was used to analyze the humoral antifibrosarcoma background of BALB/c mice. Sera from normal BALB/c mice showed increased cytotoxic activity with age when tested on the teflon-induced fibrosarcoma Fisa-T7. Sera from (a) untreated, (b) thymectomized, or (c) thymectomized and irradiated 3-month-old mice showed different levels of cytotoxic activity. T-deprived mice had levels found only in 40-wk-old untreated mice. Sera from 3-month-old female mice, untreated or T-deprived, and from 14-month-old mice were tested for cytotoxicity on BALB/c Fisa-T7 fibrosarcoma, C57Bl/6J EL4 lymphoma, and BALB/c thymus cells. The T-deprived mice showed increased serum cytotoxicity for the fibrosarcoma and lymphoma but not for the thymus cells. Serum activity for all three cells was demonstrated in the 14-month-old mice. Four-month-old T-deprived mice showed a higher degree of resistance than intact mice when challenged with two different fibrosarcomas. A direct correlation between tumor growth and antitumor antibodies was found in 14-month-old female mice when they were challenged with Fisa-T7 cells. (34 refs.)

77-0321 **Natural Anti-Tumor Serum Reactivity in BALB/c Mice. II. Control by Regulator T-Cells.** (Eng.) Colnaghi, M. I. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy) Menard, S.; Della Porta, G. *Int J Cancer* 19(2): 275-280; 1977.

A natural humoral cytotoxic reactivity detected in the serum

of BALB/c mice against fibrosarcoma cells is described. Complement-dependent cytotoxicity assays were used to test the sera of 37 female BALB/c mice from 1 to 18 mo of age for natural response to BALB/c fibrosarcoma Fisa-T7 and BALB/c thymus cells. The natural response was found to increase with age. There was no correlation between the level of antitumor and antithymus antibodies. Three-month-old mice demonstrated an individual variability of the serum level of both types of antibodies. This variability also increased with age. Tests on sera from five 3-mo-old untreated BALB/c mice and five T-deprived BALB/c mice showed a higher cytotoxicity level in the sera of the T-deprived mice. Further tests were conducted to determine if a correlation existed between the level of T cells and the level of antitumor and antithymus antibodies. Old BALB/c mice had a high individual variability of T-cell level. High levels of antitumor antibodies were detected in mice with low numbers of T cells. Antithymus activity was found only in mice with a T-cell count of $> 20\%$. Injections of T cells from younger mice to older mice resulted in a decrease of the antitumor response and an increase in the antithymus response. The results suggest the existence of homeostatic balanced systems of tumor control. (18 refs.)

- 77-0322 Passive Transfer of Systemic Tumor Immunity with Cells Generated In Vitro by a Secondary Immune Response to a Syngeneic Rat Gross Virus-Induced Lymphoma.** (Eng.) Bernstein, I. D. (Dept. Pediatrics, Univ. Washington Sch. Medicine, Seattle, WA 98195) *J Immunol* 118(1): 122-128; 1977.

The ability of spleen cells obtained from W/Fu rats 4-6 wk after primary immunization with 10^7 syngeneic Gross virus-induced lymphoma (C58NT)D cells to transfer tumor immunity to nonimmune recipients was determined. A total of 75×10^6 spleen cells obtained from these animals was injected systemically by the intracardiac route into nonimmune recipients. The animals were challenged immediately thereafter with 10^6 (C58NT)D cells injected sc into the flank. These immune spleen cells induced partial but not complete suppression of tumor growth. Cells from animals that were restimulated with tumor cells did not transfer effective antitumor immunity. After in vitro sensitization, immune lymphoid cells were able to suppress tumor growth completely in passively immunized animals. As few as 5×10^7 in vitro sensitized cells allowed complete inhibition of 10^6 (C58NT)D cells and also allowed inhibition of the growth of 10^7 (C58NT)D-F (a variant) cells, which were lethal to control animals. Immune cells that were sensitized in vitro and that could transfer immunity to the (C58NT)D cells did not transfer immunity to an antigenically unrelated tumor. The specificity of the passive immunity was demonstrated by the failure to inhibit growth of a polyoma virus-induced sarcoma in rats that inhibited growth of the Gross virus-induced lymphoma cells. Passive transfer of immune spleen cells following in vitro cocultivation with mitomycin-treated (C58NT)D cells permitted inhibition of growth of a sc inoculum of lymphoma cells. The results showed a marked increase in the

ability of immune cells, after in vitro sensitization of tumor cells, to transfer systemic tumor immunity to a nonimmune recipient. (19 refs.)

- 77-0323 Histology of Bronchial Carcinoma and Regional Lymph Nodes as Putative Immune Response of the Host to the Tumor.** (Eng.) DePaola, M. (Istituto Patologia Chirurgica II, Università di Roma, Italy) Bertolotti, A. Colizza, S.; Coli, M. *J Thorac Cardiovasc Surg* 73(4): 531-537; 1977.

A total of 242 patients who had bronchial carcinoma and who underwent radical surgery were assessed to determine putative host resistance to the tumor at the histological level. The degree of lymphocytic infiltration in the center and around the tumor, plus the degree of sinus histiocytosis and follicular hyperplasia in the regional lymph nodes, were scored. The sum of these two scores was taken to represent the host defensive factor, which was then divided into three grades (D-, D+, and D++). The 5-yr survival rate of the reaction-absent or poor (D-) group was much lower than that of the reaction-present (D+) and strong-reaction-present (D++) groups. The difference was highly significant. There was no significant difference in 5-yr survival rates among histological types (squamous, adenocarcinoma, or undifferentiated) both for the D- and for the D+ and D++ groups, even though the undifferentiated type had a better prognosis in both groups. D grade was related to the incidence of metastases in regional lymph nodes. This was 48.9% for D-, 32.0% for D+, and 25.0% for D++. The 5-yr survival was plotted against presence or absence of metastases in regional lymph nodes. Spreading of the tumor in the nodes affected survival in the three groups, but survival rates among Group D- patients with negative nodes were worse than among Group D+ patients with positive nodes. The incidence of metastases in regional nodes and 5-yr survival rates are related to the putative host resistance against the tumor. (18 refs.)

- 77-0324 Production of Cytotoxic Antibody to a Benz(a)pyrene-Induced Sarcoma in Mice Receiving Xenogeneic Antitumor Immune RNA.** (Eng.) Fritze, D. (Medizinische Universitätsklinik, Bergheimerstr. 58, D-6900 Heidelberg, W. Germany) Kern, D. H.; Chow, N.; Pilch, Y. H. *Cancer Immunol Immunother* 1(4): 245-250; 1976.

The production of cytotoxic antibody to a benz(a)pyrene-induced sarcoma (BP-1) in C3H mice inoculated sc and ip over a 2-wk period with xenogeneic immune RNA (I-RNA) was studied. I-RNA was extracted from the lymphoid organs of female Hartley guinea pigs after they had been immunized with normal C3H cells or tumor cells from a spontaneous mammary carcinoma (SMT), a BP-I, or a methylcholanthrene-induced sarcoma (MC-1). Sera from mice inoculated with BP-1 I-RNA exhibited significantly more cytotoxic activity for BP-1 sarcoma target cells from passage 32 and BP-1 sarcoma target cells from passage 73 than did normal C3H

serum or sera from mice treated with any of the other I-RNAs. However, when all sera were tested on MC-1 sarcoma target cells from passage 52, sera of mice injected with BP-1 I-RNA showed the same cytotoxic activity as normal C3H serum or sera from mice treated with any of the other I-RNAs. The active BP-1 serum was absorbed with C3H spleen cells and MC-1 or BP-1 sarcoma cells. Absorption with BP-1 sarcoma cells removed much more cytotoxic activity from BP-1 serum than absorption with identical numbers of MC-1 sarcoma cells or C3H spleen cells. Administration of xenogeneic antitumor I-RNA to normal mice may mediate a humoral immune response directed against tumor-associated antigens. It is tempting to speculate that the I-RNAs extracted from the lymphoid organs of guinea pigs after immunization with mammary carcinoma cells or normal C3H tissues failed to induce cytotoxic antibodies to BP-1 sarcoma cells because these tissues contained antigens not shared by BP-1 sarcoma cells. However, the results are inconclusive. (41 refs.)

77-0325 Tumor-Associated Lymphoid Cells: Analysis of Host Cells That Bind to Syngeneic and Allogeneic Tumor Cells Shortly After Tumor Administration. (Eng.) Schick, B. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel) *Transplant Proc* 9(1): 1157-1160; 1977.

The serological and functional characteristics of syngeneic and allogeneic tumor-associated peritoneal exudate lymphocytes (PEL) that bind to and lyse tumor cells shortly after tumor administration were studied. Following injection of irradiated EL-4 ip, PEL from syngeneic C57BL/6 and allogeneic BALB/c mice were prepared. In vitro cytolytic activity against EL-4 was detected in PEL 3 days after injection. Activity increased until day 5 (syngeneic) and day 6 (allogeneic) and then decreased. The max binding of syngeneic PEL to EL-4, as assayed by conjugate formation, occurred on day 5, which corresponded with the max cytotoxic activity of the PEL. In allogeneic PEL, the time course of conjugate formation paralleled killing activity. The binding capacity of syngeneic PEL with EL-4 was elevated significantly as a result of immunization against irradiated EL-4. PEL were predominantly θ -bearing cells that lacked detectable surface immunoglobulin. Almost 95% of the small syngeneic and allogeneic PEL that bound to EL-4 tumor cells were positively stained with anti- θ and fluoresceinated goat antisera to mouse 7S globulin. Immune processes involving host lymphocytes can thus be examined as early as 3 days after tumor inoculation. (11 refs.)

77-0326 Immunologic Unresponsiveness of Mouse Spleen Sensitized to Allogeneic Tumors. (Eng.) Argyris, B. F. (Dept. Microbiology, S.U.N.Y., Upstate Medical Center, Syracuse, NY 13219) *Cell Immunol* 28(2): 390-403; 1977.

Spleen cells from C57BL/6 mice, sensitized for 15 days with

one ip injection of 25×10^6 allogeneic P-815 mastocytoma cells, were hyporesponsive in a 4-day mixed lymphocyte culture (MLC) with DBA/2 or AKR as stimulating spleen cells. When 5×10^5 tumor-sensitized cells were stimulated with either 1 μ g concanavalin A or 20 μ g lipopolysaccharide, mitogen responsiveness did not appear suppressed. Gradual recovery of MLC reactivity began around 60 days postsensitization, and normal reactivity was regained after 3 mo. Spleen cells from mice sacrificed at 15 and 2 days after sensitization exhibited the highest in vitro cytotoxicity, but cells from mice sacrificed at 10 days failed to generate cytotoxic cells because these mice had not completely rejected the tumor allograft. When cells were reexposed in vitro to DBA/2 stimulating spleen cells, more cytotoxic cells were generated, indicating a secondary response. MLC reactivity of tumor-sensitized spleen cells could not be restored by absorption on glass, filtration through a nylon wool column, treatment with anti θ , antimacrophage, or anti-immunoglobulin serum, or centrifugation on a bovine serum albumin-density gradient. Absorption of sensitized spleen cells on DBA/2 spleen or spleen monolayers treated with mitomycin C reduced cytotoxicity sharply but did not reverse MLC responsiveness, indicating that suppressor and cytotoxic activity can be separated from each other. Since the suppressor cell does not appear to be a macrophage or B cell, perhaps it is a noncytotoxic T cell. (22 refs.)

77-0327 Enhancement of Tumor Growth by Syngeneic Spleen Cells from Aged Mice (Meeting Abstract). (Eng.) Gozes, Y. (Weizmann Inst. Science, Rehovot, Israel) Trainin, N. *Isr J Med Sci* 12(10): 1238; 1976. (no refs.)

77-0328 Anti-tumour Immunity by Normal Allogeneic Blood Transfusion in Rat. (Eng.) Oikawa, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Japan) Hosokawa, M.; Imamura, M.; Sendo, F.; Nakayama, M.; Gotohda, E.; Kodama, T.; Kobayashi, H. *Clin Exp Immunol* 27(3): 549-554; 1977.

When female WKA/MK rats were preimmunized with a single iv injection of 2 ml whole blood from normal allogeneic Donryu rats 7 days prior to sc challenge with 1×10^5 KMT-17 tumor cells, tumor growth was inhibited and 14/21 rats survived. Whole blood from syngeneic rats did not inhibit tumor growth, and the difference in survival between the two groups was statistically significant ($p < 0.05$). The inhibitory effect was also observed in WKA/MK rats immunized with WBC, RBC, and platelets from Donryu rats. An inhibitory effect was also seen in rats immunized once with whole blood from Kyoto, Tokyo, and Fischer rats. Strong inhibition was obtained with Kyoto rat blood. All nine animals immunized with ACI/N rat blood died of tumor. These data show that the graft-versus-host reaction may not contribute to the inhibitory effect, because the effect was obtained by immunization with mitomycin C-treated allogeneic WBC and also by immunization with F_1 hybrid whole blood. It is concluded

that the inhibition may be due to nonspecific active immunization. The significance of blood transfusion with special reference to clinical immunotherapy of cancer patients is discussed. (21 refs.)

- 77-0329 Immunologic Studies in Contacts of Osteosarcoma in Humans and Animals.** (Eng.) Singh, I. (Div. Orthopaedics, Dept. Surgery, Medical Coll. Ohio, Post Office Box 6190, Toledo, OH 43614) Tsang, K. Y.; Blake-more, W. S. *Nature* 265(5594): 541-542; 1977.

Immunologic investigations in contacts of osteosarcoma in animals and humans are presented. Tumor-specific antibodies were demonstrable against osteosarcoma imprints by immunofluorescence in the sera of 83% of tumor-bearing newborn hamsters, and 87% of the sera from these animals reacted positively against TE-85 cells from a patient with osteosarcoma. In control animals, only 4% had sera that reacted positively against osteosarcoma imprints and TE-85 cells. The percentage inhibition of TE-85 target cells by the lymphocytes from household contacts of a patient with osteosarcoma of the femur, five patients with osteosarcoma, and normal individuals was determined. Significant inhibition by the lymphocytes was observed in 5/6 household contacts, all of the patients with osteosarcoma, and one of the nine normal individuals. In the animal model, hamster mothers had lymphocytes that exhibited significant cytotoxicity against TE-85 cells at day 20. The lymphocytes from the same mothers exhibited minimal cytotoxicity before the injection of cells into newborn hamsters and on day 5 after cell injection. The results of the lymphocyte microcytotoxicity test on tumor-bearing hamsters on day 20 demonstrated that 75% of the animals showed a significant cytotoxic effect against the target cells. Only 4% of the controls demonstrated a significant reaction. The results support the hypothesis that an agent is responsible for transmission of horizontal immunity to close contacts of patients with spontaneously arising osteosarcoma. (6 refs.)

- 77-0330 Antisera Against Leukaemia-associated Antigens on Human Lymphocytes.** (Eng.) Hsu, C. C. (Dept. Medicine, Northwestern Univ. Medical Center, 303 E. Chicago Ave., Chicago, IL 60611) Marti, G. E.; Mittal, K. K. *Clin Exp Immunol* 27(3): 487-496; 1977.

Antisera reacting with human leukemic lymphocytes prepared by immunizing rabbits with untreated leukemic lymphosarcoma cells having the surface characteristics of both T and B cells are described. After absorption with WBC, RBC, and serum proteins from normal individuals, the antisera demonstrated significant complement-dependent cytotoxicity against leukemic cells from patients with acute lymphoblastic leukemia (ALL: 9/11 patients), leukemic lymphosarcoma (7/9), and chronic lymphocytic leukemia (CLL: 9/12), with an antibody titer of 1:64 or greater. The antisera did not react with blood lymphocytes from healthy

individuals or patients with nonlymphoproliferative disorders or with leukemic cells from patients with acute myeloblastic or chronic granulocytic leukemia. The antisera did react with possible common antigens on tonsillar lymphocytes, B-lymphoblastoid cell lines, and some blood lymphocytes from patients with infectious mononucleosis. The cytotoxicity of the antisera against lymphoblastoid and tonsillar cells was inhibited by ALL and CLL cell lysates but not by a cell lysate from normal lymphocytes; it was neutralized by goat antirabbit immunoglobulin G. These findings suggest that the antisera contained antibodies reactive with antigens possibly common to neoplastic lymphocytes, tonsillar cells, lymphoblastoid cells, and some blood lymphocytes from patients with infectious mononucleosis. (52 refs.)

- 77-0331 Host-Tumor Relationships and Immediate Hypersensitivity Reactions.** (Fre.) Lynch, N. R. (Laboratoire d'Immunopathologie, B. P. 8, 94800 Villejuif, France) Salomon, J. C. *Ann Immunol (Paris)* 128C(1/2): 121-123; 1977.

The effect of inducing an intratumoral passive anaphylactic reaction on the uptake of iv Lissamine green (an intracellular dye) and on labeled spleen cells was studied in methylcholanthrene-induced tumors in C3H mice. The anaphylaxis was induced by an intratumoral injection of the immune serum antialbumin, prepared from DBA mice. After anaphylaxis, tumor cell levels of the dye and the radioisotopes were higher than those in muscle, intestinal, and peritoneal cells. The increase was attributed to augmentation of capillary permeability. An antitumor effect, inhibited by cyproheptadine, was observed after repeated intratumoral antialbumin injections, and the antitumoral activity of BCG was also enhanced. IgE levels were not increased in C3H mice grafted with a methylcholanthrene-induced tumor after treatment with the immunostimulants *Corynebacterium parvum*, *Bordetella pertussis*, and BCG. In addition, anaphylactic reactions to systemic antialbumin and sensitivity to the vasoactive amines histamine and serotonin were inhibited in these animals. (4 refs.)

- 77-0332 In Vivo and In Vitro Effects of Acute Graft-Versus-Host Serum in the Rat.** (Eng.) Cianciolo, G. J. (Dept. Microbiology, Univ. Miami Sch. Medicine, Miami, FL 33152) Jensen, J. A. *Transplantation* 23(4): 303-309; 1977.

The effects of serum from rats undergoing acute local graft-versus-host (GVH) reactions on immune response were studied in vivo and in vitro. Compared with normal F₁ serum, pooled serum from 6- to 8-wk-old female Lewis × Brown Norwegian F₁ hybrid rats undergoing acute local GVH reactions increased node wt in a popliteal lymph node wt gain assay in syngeneic animals. Injection of donor cells in normal F₁ serum in the left rear footpad and corresponding concentrations of donor cells in GVH serum in the right rear footpad resulted in an increase in popliteal node wt of 28.8% on the

GVH side. Fifty of the 64 animals tested had larger nodes on the GVH serum side. Preinjection of the serum into the footpads 2 hr before donor cells and injection of the serum also resulted in increased node wt. In in vitro tests, GVH serum inhibited the blastogenic responses of syngeneic and allogeneic cells to alloantigens and phytohemagglutinin P. The relationship between the increased response seen in vivo and the inhibition found in vitro is not yet clear. (17 refs.)

77-0333 Reduction of Fatal Graft-Versus-Host Disease by ^3H -Thymidine Suicide of Donor Cells Cultured with Host Cells. (Eng.) Cheever, M. A. (Div. Oncology, Dept. Medicine, Univ. Washington Sch. Medicine, Seattle, WA 98195) Einstein, A. B.; Kempf, R. A.; Fefer, A. *Transplantation* 23(4): 299-302; 1977.

The effect of the ^3H -thymidine (^3H -TdR) suicide technique on the ability of donor cells to induce fatal graft-versus-host disease (GVHD) was studied in BALB/c mice. C57BL/6 (H-2b) spleen cells were stimulated in vitro with irradiated BALB/c (H-2d) Moloney lymphoma cells in mixed culture, and a pulse of high-specific-activity ^3H -TdR was added 24 hr later to eliminate proliferating cells. After 16 hr more of culture, the cells were harvested. The viable cells were counted and used in the assay for lethal GVHD by injecting them iv into adult BALB/c mice immunosuppressed with cyclophosphamide (180 mg/kg). These cells induced fatal GVHD in fewer mice (52%) than did C57BL/6 cells cultured with BALB/c lymphoma cells but without ^3H -TdR (87%) or C57BL/6 cells cultured with irradiated C57BL/6 cells with (95%) and without ^3H -TdR (86%). These results rule out a nonspecific cytotoxic effect of ^3H -TdR on cultured cells and indicate that the ^3H -TdR suicide technique greatly diminishes the ability of cells to induce lethal GVHD. (22 refs.)

77-0334 Depression of the Platelet Count after Inoculation of Mice with L1210 or L5178Y Cells. (Eng.) Hacker, M. (St. Jude Children's Res. Hosp., 332 N. Lauderdale, P.O. Box 318, Memphis, TN 38101) Roberts, D.; Jackson, C. *Br J Haematol* 35(3): 465-471; 1977.

Female C57BL/6 \times DBA/2 mice were inoculated with L1210 or L5178Y leukemia cells either iv or ip. L1210 cells caused a reduction in circulating platelets as early as 24 hr after inoculation. The onset in reduction was related to the number of cells injected, but once the reduction was initiated, the rate of decrease was independent of inoculum size. Significant numbers of red cells were present in ascites fluid by day 4 after inoculation and continued to accumulate for several days before death. After ip inoculation, the platelet count remained more or less constant at 400×10^9 /liter from day 3 until death. The platelet count was depressed to 100×10^9 /liter after iv inoculation, but ip bleeding did not occur. Injection of L5178Y cells by either route caused an initial decrease, but the platelet count recovered to 80% of normal on days 9 and 10 before becoming markedly depressed prior to death of the host. Implantation of diffusion chambers con-

taining L1210 cells also decreased the platelet count, which later returned to normal. These findings indicate that death of animals after ip inoculation cannot be entirely attributed to ip hemorrhage. (8 refs.)

77-0335 Correlation Between Tumour Stage, Tumour Grade, and Immunocompetence in Patients with Carcinoma of the Bladder and Prostate. (Eng.) Adolphs, H. D. (Dept. Urology, Saint Antonius-Hosp., Postfach 135 5, D-5180 Eschweiler, W. Germany) Steffens, L. *Eur Urol* 3(1): 23-25; 1977.

Cellular immunocompetence was evaluated in 83 patients with prostatic carcinoma and 132 patients (101 men, 31 women) with transitional cell bladder carcinoma with reference to tumor grade and stage by the cutaneous dinitrochlorobenzene (DNCB) hypersensitivity reaction. In papillary transitional cell bladder carcinoma, there was a significant correlation between the grade of malignancy and tumor spread. With increasing local or metastatic spread, the degree of lack of histologic differentiation also increased. Due to the high degree of correlation, the effect of stage and grade on the reduction of immunocompetence (DNCB negativity) could not be determined separately; however, the connection between DNCB negativity and tumor stage and grade combined was definite. In prostatic carcinoma, there was also a significant correlation between stage and grade, but to a lesser degree than that in bladder carcinoma. The reduction of immunocompetence was substantially more dependent on the stage than on the grade of malignancy. A knowledge of the correlation between immunocompetence and tumor stage and grade is of great significance. (21 refs.)

77-0336 Evaluation of Specific Cellular Immunity During the Evolution of Breast Cancer. (Fre.) Lamoureux, G. (Centre de Recherche en Immunologie, Institut Armand-Frappier, Laval, Quebec, Canada) Poisson, R. *Ann Immunol (Paris)* 128C(1/2): 107-108; 1977.

The number of circulating T lymphocytes and aspects of their function were studied in breast cancer patients, 45 patients with benign breast tumors, and 154 controls. The breast cancer patients were divided into three groups based on tumor evolution: (1) T1-T4, NO + MO (47 patients); (2) T1-T4, N⁺ + MO (75); and (3) T1-T4, N⁺ + M⁺ (50). The percentage of circulating T lymphocytes was < 10% in 18.4% of the cancer patients but in only 13% of the patients with benign tumor and 4% of the controls. A significant ($P < 0.1$) decrease in T lymphocyte blast transformation by phytohemagglutinin (PHA) was observed in the cancer patients (5.7) compared to controls (11.8). Concanavalin A (Con A) transformation was even more significantly reduced ($P < 0.001$) in the cancer patients (5.5) compared to controls (9.5). A difference in blast transformation values was observed in the three groups of cancer patients. Delayed sensitivity reactions to four antigens, purified protein derivativ e

of tuberculin (PPD), candidin, a viral extract, and streptokinase-streptodornase, were markedly diminished in the N^+ -MO and N^+ -M⁺ cancer patients, compared to patients with benign tumors and controls. Response to Con A seems to be sufficiently sensitive for use as a means of screening breast cancer patients. (no refs.)

- 77-0337 **Suppression of the Humoral Immune Response by Plasmacytomas: Mediation by Adherent Mononuclear Cells.** (Eng.) Kolb, J. P. (Veterans Admin. Hosp., 408 First Ave., New York, NY 10016) Arrian, S.; Zolla-Pazner, S. *J Immunol* 118(2): 702-709; 1977.

Female Balb/c and male (Balb/c x A/J) F₁ (CAF₁) mice bearing sc plasmacytomas have a severely impaired ability to mount a primary immune response, although T cells from these mice appear to function normally by both in vivo and in vitro criteria. Studies showed that depressed immune response appeared to be regulated by a cell population found in the spleens and peritoneal cavities, but not in the lymph nodes or thymuses. The number of suppressor cells was directly proportional to the size of the plasmacytoma. Their suppressive activity was restricted, in that they did not affect the proliferative response of normal spleen cells to either phytohemagglutinin or 8-bromo-guanosine-3',5' monophosphate. The suppressor cells were radioresistant, and they adhered to Sephadex G-10 columns, nylon wool columns, and plastic. They lacked surface immunoglobulins and thymus-associated antigens. These data support the previously reported hypothesis that the suppressor cell is a macrophage. The results also suggest that plasma cell tumors indirectly induce an impairment in the host humoral immune response by stimulating the expression of regulatory functions in a population of splenic and peritoneal macrophages. (47 refs.)

- 77-0338 **Antitumor Immunity Against a Syngeneic Polyoma-Virus-Induced Sarcoma, Accompanied by High Levels of Cytotoxic Antitumor Antibodies (Meeting Abstract).** (Eng.) Ran, M. (Tel Aviv Univ., Tel Aviv, Israel) *Isr J Med Sci* 12(10): 1238; 1976. (no refs.)

- 77-0339 **Human Polymorphonuclear Leucocytes as Mediators of Antibody-Dependent Cellular Cytotoxicity to Herpes Simplex Virus-Infected Cells.** (Eng.) Oleske, J. M. (Dept. Pediatrics, New Jersey Coll. Medicine, Newark, NJ 07100) Ashman, R. B.; Kohl, S.; Shore, S. L.; Starr, S. E.; Wood, P.; Nahmias, A. J. *Clin Exp Immunol* 27(3): 446-453; 1977.

Antibody-dependent cellular cytotoxicity (ADCC) against target cells (Chang liver cells, CL) acutely infected with type 1 herpes simplex virus was mediated by human polymorphonuclear leukocytes (PML). Higher concentrations of immune serum and more time were required in the reaction

mediated by PML than in that mediated by human mononuclear cells (MC). In addition, the percent of PML-mediated ADCC was lower than MC-mediated ADCC at the same ratio of effector to target cells. Cytolysis mediated by both PML and MC was consistent with "one hit" probability predictions. This result suggests that target cell death results from an interaction with a single effector cell. The calculated frequency of effector cells for both PML and MC was similar, approx 3.5%. Preliminary examination of the nature of effector cells suggests that they were not a morphologically distinct subclass of PML. These studies may point to a possible new role for PML in host defense against viral infections. (2 refs.)

- 77-0340 **Tumour-specific Antibodies Reactive with Cell Surface Antigens in Children with Wilms' Tumour.** (Eng.) Kumar, S. (Immunology Lab., Medical Sch Univ. Manchester, Manchester, England) Waghe, M.; Taylor, G. *Int J Cancer* 19(3): 351-355; 1977.

Tumor-specific antibodies directed against membrane antigens were studied by immunofluorescence in children (4 mo-14 yr; mean 4.5 yr) with Wilms' tumor. Only 3/45 tumor patients had demonstrable tumor-specific antibody directed against cell surface antigens. None of the three reacted with either normal or fetal kidney cells, even in the unabsorbed state. Two sera from the Wilms' group had antibody that reacted with Wilms' tumor cells but not renal cells and was absorbable with skin fibroblasts. Antibody that was capable of collaborating with K cells to kill Wilms' target cells was found in only 2/45 children suffering from this tumor. No patient possessed tumor-specific antibody out of 27 children (3 mo-12 yr; mean 4.1 yr) with nonrenal solid tumors and 52 age-matched controls (7 mo-14 yr; mean 4.8 yr). No patient exhibited both K-cell collaborating antibody and membrane immunofluorescence. This finding, which is rather surprising, suggests that the immunoglobulin classes involved may be different. Further investigations are clearly necessary. (10 refs.)

- 77-0341 **Cytotoxic Antibodies to Human Leukaemia Cells in Normal Human Sera.** (Eng.) Dore, J. F. (Laboratoire d'Immunologie et de Cancerologie Experimentale, Centre Leon Berard, 28 rue Laennec, 69373 Lyon Cedex 2, France) Guibout, C.; Bertoglio, J.; Liabeuf, A. *Biomedicine* 25(10): 382-384; 1976.

Complement-dependent antibodies cytotoxic to leukemia cells were investigated in the sera of parents of leukemic children and from normal unimmunized blood donors. The sera were tested in a microcytotoxicity assay against the leukemic cells of the children and against the remission cells. Sera from the father of an 8-yr-old girl with acute myeloblastic leukemia, reacted widely with cells from both acute lymphoid and myeloid leukemias. At least two antigens were detected. The sera from the father of a 2-yr-old boy with acute lymphoblastic leukemia was specific for that leukemia. The sera from

in apparently normal 47-yr-old healthy blood bank donor was also specific for acute lymphoblastic leukemia. The presence of antibodies reactive with tumor cells in relatives of leukemic patients may suggest that they have been exposed to an infectious agent. (12 refs.)

77-0342 Detergent Solubilization and Partial Purification of Tumor Specific Surface and Transplantation Antigens from SV40-Virus-Transformed Mouse Cells. (Eng.) Chang, C. (Macromolecular Biology Section, NCI, NIH, Bethesda, MD 20014) Pancake, S. J.; Luborsky, S. W.; Mora, P. T. *Int J Cancer* 19(2): 258-266; 1977.

Detergent solubilization in .5% Triton X-100 was used to recover SV40-induced tumor-specific surface antigen (TSSA) and tumor-specific transplantation antigen (TSTA) from SV40-transformed mouse cells. TSSA activity was measured by a serum-mediated microcytolytic assay. TSTA activity was determined by in vitro experiments using BALB/c mice challenged ip with mKSA-ASC cells. Yields of approx 50% TSSA were obtained in SV AL/N whole cell extracts and in ammonium sulfate precipitation fractions of the extracts. Sephadex G-150 chromatography of a 30%-50% ammonium sulfate fraction resulted in the separation of two TSSA-active fractions: one that eluted near the void volume, the other near the apparent molecular wt (45,000). Whole cell extracts and fractions from a spontaneously-transformed mouse cell line (T AL/N) had no significant inhibitory activity. The various TSSA active fractions were also significantly active in immunizing BALB/c mice challenged by SV40 tumorigenic mKSA-ASC cells (cell dosage = 10^6 ; $p < .002$). However, mKSA-ASC cells caused lethal tumors in the control mice. The investigators concluded that detergent extraction provided stable and partly dissociated antigens suitable for further study. (30 refs.)

77-0343 Nuclear Preparations of SV40-Transformed Cells Contain Tumor-Specific Transplantation Antigen Activity. (Eng.) Anderson, J. L. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014) Martin, R. G.; Chang, C.; Mora, P. T.; Livingston, D. M. *Virology* 76(1): 420-425; 1977.

The specificity of nuclear tumor-specific transplantation antigen (TSTA) activity in preparations of partially purified tumor antigen (TA) from simian virus 40 (SV40)-induced tumor cells was tested in in vivo tumor-rejection experiments in Balb/c female mice. Mice were inoculated with TA purified through chromatography on agarose on days 0 and 7 and challenged ip on day 17 with one of three tumor lines: (1) mKSA, an SV40 Balb 3T3-derived line; (2) Adj-PC-5, a non-SV40 line induced by adjuvant injection in Balb/c mice; and (3) Meth-1-A, a methylcholanthrene-induced murine line. At each purification step, animals injected with TA-enriched fractions were completely or nearly completely protected against mKSA tumor challenge by 18 and 3 complement-fixing (CF) units, but only partially (10%-50%) protected by

0.5 CF unit. TA-depleted fractions from the ammonium sulfate and agarose purification steps were significantly less active for TSTA than the respective TA-enriched fractions. A pool of all the TA-depleted fractions after chromatography on DEAE-cellulose, however, apparently contained some TSTA activity. It is concluded that nuclei of SV40-transformed cells contain considerable levels of TSTA activity. This activity is SV40-specific and does not appear to represent contamination by plasma membranes or virus. The results suggest two possibilities: (1) TSTA and TA activities may be contained on distinct though related molecules that copurify or (2) the TSTA activities retained in the more purified TA preparations may be contained in the TA polypeptide itself. (34 refs.)

77-0344 Molecular Relationship Between H-2 and ML Antigens on Leukaemia L-1210/v Cells. (Eng.) Strzadala, L. (Inst. Immunology and Experimental Therapy, Czerska 12, 53-114 Wroclaw, Poland) Steuden, J.; Radzikowski, C. *J Immunogenet* 4(1): 29-33; 1977.

The molecular relationship between H-2 antigens and mammary leukemia (ML) antigen at the surface of leukemic L-1210/v cells was studied by the lysostrip method. The private antigens of the H2d haplotype were present on two different populations of molecules on the leukemic cells. Pretreatment of L-1210/v cells with anti-H-2K.31 serum induced resistance to subsequent lysis with this antiserum in the presence of complement, but not to anti-H-2D.4 serum and complement. L-1210/v cells rendered resistant to anti-ML serum and complement by pretreatment with this serum and goat serum to mouse 7S globulin (GAMIG) were still fully susceptible to cytotoxic killing by anti-H-2K.31 or anti-H-2D.4 serum and complement. This demonstrates that the ML antigen is present on molecules distinct from those carrying H-2K.31 and H-2D.4 private specificities. (8 refs.)

77-0345 Studies on H-2 Specificities on Mouse Tumour Cells by a New Microradioassay. (Eng.) Garrido, F. (Tissue Immunology Unit, London Hosp. Medical Coll., London E1 2AD, England) Schirrmacher, V.; Festenstein, H. *J Immunogenet* 4(1): 15-27; 1977.

Seven mouse tumor cell lines were tested for the expression of surface alloantigens using 24 well-defined H-2 alloantisera and anti-Thy 1.2. A new radioassay was used that involves antibody-complement treatment of the tumor target cells, followed by postlabeling of the surviving tumor cells with 14 C-thymidine. The tumor cell lines were chemically induced P815 Y mastocytoma propagated in DBA/2 and EL4 lymphoma propagated in C57BL/6, a Moloney virus-induced leukemia from A/Jax mice, a Moloney virus-induced lymphoma in BALB/c mice, urethane-induced lymphoma from BALB/c mice, a Graffi virus-induced lymphoma from C57BL/6, and a Moloney virus-induced leukemia from C57BL/6 mice. With a relatively high frequency, the anti-H-2 sera reacted differently with the tumor cells than with re-

spective syngeneic lymphoid cells. Thirty-six anomalous reactions were detected in the 129 investigated. Absorption experiments performed with H-2 antigen-positive or negative lymphoid cells revealed a striking similarity between these extraspécificities and the H-2 specificities of foreign haplotypes. The theory of derepression may explain how H-2 like specificities appear on tumor cells. This implies the permanent presence in the cell's genome of a complete set of genetic information for H-2 antigens, the majority of which are normally repressed. Interference in this genetically stable control mechanism by various agents could lead to derepression and the appearance of new specificities on the cell surface. (26 refs.)

- 77-0346 **Antigenic Sites Implicated in Tumor Allograft Enhancement.** (Fre.) Duc, H. T. (Centre d'Immunopathologie et d'Immunologie expérimentale de l'INSERM, Hôpital Saint-Antoine, 75571 Paris Cedex 12, France) Kinsky, R. G.; Voisin, G. A. *Ann Immunol (Paris)* 128C(1/2): 19-20; 1977.

The complexity of transplantation antigens in the mouse has raised the question of the relative importance of serologically defined (SD) antigens (coded by the H area of histocompatibility or MHC) compared to the mixed lymphocyte (LD) reaction antigens (coded by the I region of MHC) in the immunologic promotion of tumor graft growth. Alloimmune sera were prepared by inoculating CBA mice with spleen or thymus cells or by two consecutive skin grafts of A/Jax origin. The CBA sera had similar growth-enhancing ability for the SaI (A/Jax) sarcoma in CBA mice, even though thymic cells are very poor in Ia antigen content. Similar results were obtained with DBA2 anti-C57B1/6 sera against the EL4 lymphoma. All sera contained anti-SD antibodies with hemagglutinating titers (1/2,000-1/4,000) and cytotoxic titers (60%-73% of killed cells in 1:5 dilution in the presence of rabbit complement). Repeated experiments showed that in the CBA system, anti-A/Jax sera prepared from A/Jax RBC contained exclusively anti-SD antibodies with a tumor enhancing ability. (2 refs.)

- 77-0347 **In Vivo Immunogenic Activity of Different Soluble Transplantation Antigens Synthesized by Tumor and Embryonic Cells.** (Eng.) Deichman, G. I.; Kluchareva, T. E.; Vendrov, E. L. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins and held at San Diego, May 29-June 1, 1976.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): 337-347; 1976.

Studies of immunogenic activity and specificity of soluble antigens shed into the nutrient medium of cultured tumors of Syrian hamsters are presented. In vitro cultures of SV40 induced sarcoma (E-1) and spontaneous cancer of the liver of Syrian Hamsters (HT-11B) secrete different soluble trans-

plantation antigens (TSTA) into the culture medium. Shedding of these antigens from the tumor cell membrane in vivo showed a neutralization of the immunological reaction of the organism to tumor antigens. TSTA was shown to be thermolabile, with total inactivation occurring after incubation at 56 C for 30 min or at 4 C for 6 hr. Culture preparations containing TSTA rapidly lost immunogenic activity. Animals inoculated with culture fluids prepared from 3-5-day-old E-1 and HT-11B cultures developed antitumor resistance in more than half the cases. In some animals no resistance was elicited, but instead a significant enhancement of tumor growth was observed. The factor responsible for the enhancement was not specific for a particular tumor. Immunization of animals with culture preparation from HT-11B culture enhanced the in vivo growth not only of this tumor but also of tumor E-1 and vice versa. Two or more types of antigen accumulated in the culture fluid of HT-11B and E-1 cultures; one is very labile and is responsible for specific antitumor immunity, and the other is a cross-reacting antigen responsible for the enhancement of tumor growth. (8 refs.)

- 77-0348 **Human Sarcoma-Associated Tumor Antigen.** (Eng.) Burk, K. H.; Lichtiger, B.; Trujillo, J. M.; Drewinko, B. In: *Onco-Developmental Gene Expression.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 477-484; 1976.

To demonstrate sarcoma-associated tumor antigen (SATA) on T₂ cells, indirect immunofluorescence was used to screen sera from patients with sarcoma, nonsarcoma neoplasias, and normal blood bank donors. Of 33 patients, 21 had sera positive for anti-SATA activity against the T₂ cell line (isolated from a human neurofibrosarcoma). One positive serum sample was obtained from 1 of the 20 normal and blood donors. Positive sera were absorbed to remove nonspecific, cross-reacting antibodies. Indirect immunoperoxidase electron microscopy was used to identify the subcellular localization of SATA. Cell cycle analysis of SATA expression by immunofluorescence indicated max expression in mid-G₁, which declined to minimal levels in S and G₂. Experiments with horseradish peroxidase-labeled antibody indicated that the SATA is localized on the plasma membrane. These results suggest that SATA may represent a new type of tumor-associated and/or fetal antigen, the expression of which is cell cycle-dependent. (14 refs.)

- 77-0349 **Differential Expression of Relevant Rous Sarcoma Tumor Antigens in Cultured Cells.** (Fre.) Wainberg, M. A. (Institut Lady Davis de Recherches Médicales, Centre Hospitalier "Jewish General Hosp.," Montreal, Quebec, Canada) Israel, E.; Schwartz-Luft, E. *Ann Immunol (Paris)* 128C(1/2): 101-104; 1977.

The cellular immune response of chickens with tumors induced by the Schmidt-Ruppin, Pr-B, and B-77 strains of Rous sarcoma virus (RSV) against antigens associated with

These neoplasms was studied. In cytotoxicity assays, RS cells from the wings of chickens with tumors were more susceptible to killing by spleen lymphocytes from RS-bearing chickens than were normal or in vitro RSV-transformed chick embryo fibroblasts (CEF). A comparison of the in vivo blastogenesis of lymphocytes induced by extracts or supernatant fluids of the RS tumor cells, normal cells, or RSV-transformed CEF showed the RSV-transformed CEF supernatant to be most effective. There was no significant difference in the ability of the three virus strains to induce lymphocyte transformation. The RSV-transformed CEF produced 10 times more infectious particles than the RS tumor cells. The fact that the ability to provoke a blastogenic response in circulating lymphocytes is characteristic of supernatants of cells with high viral titers indicates that the cellular immune response is directed against viral antigens. (6 refs.)

77-0350 Cell-Mediated Immunity to Herpes Simplex Virus Types 1 and 2 Antigens in Leukoplakia and Carcinoma in Man. (Eng.) Shillito, E. J. (Dept. Microbiology, Milton S. Hershey Medical Center, Hershey, PA 17033) Tarro, G.; Lehner, T. *Oncology* 33(4): 192-195; 1976.

Cell-mediated immune reactions to virion and nonvirion antigen preparations of herpes simplex virus (HSV)-1 and HSV-2 and vaccinia virus were studied in patients with oral leukoplakia (11), carcinoma (19, squamous cell), recurrent herpetic infections (4), and control subjects (5). Patients with recurrent herpes labialis or with leukoplakia showing epithelial atypia had enhanced lymphocyte proliferation; while the carcinoma patients had depressed responses. The preparation was therefore not carcinoma-specific and presumably contained virion antigen. There were significant positive correlations between the response to each of the herpes virus antigens. This suggested stimulation by an antigen common to all herpes preparations used. There was a specific increase in cell-mediated immunity to herpes virus in epithelial atypia. Separation of the nonvirion from virion antigen was necessary before specific cell-mediated immune responses to the nonvirion antigen could be assessed. (12 refs.)

77-0351 Specific Lysis of Human Colon Tumor Cells by Antibodies to CEA and Isoantigen A: Dependence on Rabbit Serum or Neuraminidase. (Eng.) Tompkins, W. A. (Center Zoonoses Comparative Medicine, Univ. Illinois, Coll. Veterinary Medicine, Urbana, IL 6180) Seth, P. B.; Yip, D.-M.; Palmer, J. L.; Gee, S. R.; Rawls, W. E. *J Immunol* 117(5): 1943-1948; 1976.

The specific lysis of human colon tumor cells (HCT-8 and HT-29) by antibodies to carcinoembryonic antigen (CEA) and isoantigen A was measured by the ^{51}Cr cytotoxicity test. In the absence of specific antibodies, 85% of the ^{51}Cr was released from HCT-8 cells by a 1:4 dilution of rabbit serum compared to 48% from HT-29 cells. When rabbit serum diluted 1:4 was utilized as a source of complement, specific

cytolysis was evident. In the case of HT-29 cells, which possess A antigen, sera from blood group B and O persons gave 84.8% and 84.6% specific release, respectively. Sera from persons with A blood group and AB blood group gave only 17.0% and 15.8% specific release, respectively. In contrast, when HCT-8 cells were used as target cells, both anti-A and anti-B antibodies caused cytolysis despite the apparent absence of A and B antigens on these cells. In the presence of guinea pig or human complement, no cytolytic activity of anti-CEA was found against any cell line. However, in the presence of rabbit complement, specific cytotoxicity was demonstrated against both CEA-producing cell lines HT-29 and HCT-8. No specific cytotoxicity was obtained with heated rabbit serum reconstituted with guinea pig sera as a source of complement. In addition, pretreatment of cells with heated rabbit serum or rabbit immunoglobulin M followed by specific antibodies and the guinea pig complement failed to cause cell lysis. Treatment of HT-29 cells with 10 units of neuraminidase (NASE) increased the cytotoxic potential of anti-CEA but not anti-A antibodies. However, treatment with 100 units NASE made the cells susceptible to anti-A as well as anti-CEA. Treatment of HCT-8 cells with either 10 or 100 units NASE resulted in specific lysis by anti-CEA. Although human complement was not effective in mediating a cytotoxic anti-A or anti-CEA reaction, anticomplement immunofluorescence indicated that the complement activation sequence was effective at least up to the C3 component. Certain tumor cells may have surface properties that render them resistant to immune lysis. (15 refs.)

77-0352 Membrane-Associated Antigen from the SV40-Induced Hamster Fibrosarcoma, PARA-7. I. Role in Immune Complex Formation and Effector Cell Blockade. (Eng.) Prather, S. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033) Lausch, R. N. *Int J Cancer* 18(6): 820-828; 1976.

The membrane-associated antigen from the simian virus 40 (SV40)-induced hamster fibrosarcoma, PARA-7, was investigated. Material extracted from PARA-7 cells with pH 9.4 glycine buffer was examined for its capacity to neutralize SV40 anti-serum-dependent spleen cell cytotoxicity. Increasing amounts of crude PARA-7 antigen were added to a constant dilution (1:1,000) of SV40 antiserum. Antibody-dependent cellular cytotoxicity (ADCC) could be neutralized, and the extent of neutralization was a function of the concentration of antigen added. No significant ADCC was noted following addition of 0.016-16.3 μg protein extract. Blocking occurred at the level of the sensitized effector cell but not at the level of the target cell. Neither the glycine buffer extract nor the medium concentrate could block the cytotoxicity of cytomegalovirus strain C-87-sensitized spleen cells for Cx-90-3B, T2 target cells. A 1:1,000 dilution of SV40 antiserum mixed with 0.5 μg PARA-7 extract could no longer mediate ADCC. When PARA-7 target cells were pretreated with this preparation, the cytotoxicity of subsequently added effector cells was significantly impaired. In contrast to

antigen alone, however, the preparation did not significantly block at the effector cell level. The blocking site of a serum pool obtained from hamsters bearing PARA-7 tumors averaging 1.1 cm in diameter and devoid of ADCC activity was examined. The serum consistently blocked only at the target cell level. Although no statistically significant blocking was observed at the effector cell level, 3/4 tests were suggestive. Single washing of the serum-treated target cells resulted in abrogation of significant blocking. Loss of serum ADCC during progressive tumor growth may be due to immune complex formation. (32 refs.)

- 77-0353 Cell Surface Antigens of Human Malignant Melanoma. III. Recognition of Autoantibodies with Unusual Characteristics.** (Eng.) Shiku, H. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Takahashi, T.; Resnick, L. A.; Oettgen, H. F.; Old, L. J. *J Exp Med* 145(3): 784-789; 1977.

Sera from three patients with malignant melanoma showing reactivity with cultured autologous melanoma cells were analyzed by mixed hemabsorption and immune adherence assays in conjunction with absorption tests. Surface antigens detected by these sera occurred on a wide range of nucleated cells, both normal and malignant, derived from human, monkey, mouse, and chicken. Absorption tests showed that each serum had a characteristic pattern of reactivity, indicating the detection of distinct antigenic systems. Auto-, allo-, and xenoreactivity, as well as the capacity to distinguish different cell populations on the same individual, were observed in two sera. The third serum reacted with an antigen that apparently is only absent on RBC. These broadly reactive antibodies may have resulted from chemotherapy. (6 refs.)

- 77-0354 Decreased "Natural Killer" Effect in Tumor-Bearing Mice and Its Relation to the Immunity Against Oncornavirus-Determined Cell Surface Antigens.** (Eng.) Becker, S. (Dept. Tumor Biology, Karolinska Institutet, S-104 02 Stockholm 60, Sweden) Klein, E. *Eur J Immunol* 6(12): 892-898; 1976.

The natural killer (NK) efficiency of spleen and blood lymphocytes was studied in male and female CBA, A, and (C57Bl × CAB)_F₁ mice bearing either transplanted methylcholanthrene- or Moloney sarcoma virus (MSV)-induced sarcomas or in athymic nude mice bearing grafts of human lymphoblastoid lines. The target cells used in the cell-mediated cytotoxicity assay were YAC and RBL-5 cells. No evidence for suppressor cells was found, although the NK effect was reduced in all three tumor systems. After regression of the MSV tumors, the activity was high again, against YAC. Against RBL-5, the effect of control spleen cells was low, but that of the MSV tumor-bearing spleen cells was high. A cytotoxic role of T cells is indicated because the anti-YAC killer cell population was enriched after it was passed through nylon wool. However, treatment with anti-Thy-1.2 serum did

not influence the effect markedly, whereas the anti-RBL activity of spleen cells from tumor-bearing (CBA × (57Bl) mice decreased after Thy-1.2-positive cells were removed. Therefore, YAC seems to be more sensitive to the NK effect and RBL-5 seems to be more sensitive to the T-cell-mediated immune effect. (19 refs.)

- 77-0355 The "Natural Killer" Cell in the Mouse Does Not Require H-2 Homology and Is Not Directed Against Type or Group-Specific Antigens of Murine (Viral) Proteins.** (Eng.) Becker, S. (Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden) Fenyo, E. M. Klein, E. *Eur J Immunol* 6(12): 882-885; 1976.

Several lymphoma lines were tested for their sensitivity to the cytolytic effect of CBA spleen cells (natural killer cells; NK) and their reactivity with antisera directed against certain C type virus-determined proteins expressed on the cell surface. All lymphoma cell lines (YAC cl 21, YALB, YACIR IM YAC462-IR, 3T3, RBL-5, F0745, and YAC-1) reacted with the anti-RVL gp69/71 and anti-p30 serum, but reactivities were variable with the anti-FV p15, anti-RLV p12, and mouse anti-Moloney cell-surface antigen serum. Since no correlation was seen between sensitivity to the NK effect and to lysis by various sera, the target for the NK cell cannot be a group-specific antigenic determinant of the viral proteins or the antigen recognized serologically by mice. Different target and effector cell combinations with regard to H-2 composition did not indicate that H-2 homology is necessary for the NK effect. (10 refs.)

- 77-0356 Demonstration of a Marek's Disease Tumor-Associated Surface Antigen (MATSA) on Six Cell Lines Derived from Marek's Disease Lymphomas.** (Eng.) Matsuda, H. (Dept. Pathology, Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita, Osaka, Japan) Ikuta, K.; Miyamoto, H.; Kato, S. *Biken J* 19(3): 119-123; 1976.

Sera from rabbits and chickens immunized with MSB-1 cells were used to test six Marek's disease (MD) lymphoblastoid cell lines (MSB-1, MOB-1, MOB-2, MOB-3, HPRS Line 1, HPRS Line 2) and MD ovarian lymphoma cells for the presence of MD tumor-associated surface antigen (MATSA). MATSA was examined by indirect membrane immunofluorescence. Rabbit anti-MSB-1 reacted with a high proportion of all six MD lymphoblastic line cells and with up to 27.0% of the ovarian lymphoma cells. The chicken anti-MSB-1 sera rarely reacted with the MD ovarian tumor cells or the six MD lymphoblastoid cell lines. These results indicate that MATSA is unrelated to known MD virus-induced antigens that are produced in the productive cycle of infection. These findings also indicate that MATSA was specifically associated with most cells of all six MD lymphoblastoid cell lines and with MD lymphoma cells in proportions varying from 9.1% to 27.0%. (17 refs.)

77-0357 An Attempt to Detect Cell Surface Antigens in Cultured Human Brain Tumors by Mixed Hemadsorption Test. First Report. (Eng.) Miyake, E. (Dept. Neurosurgery, Neurological Inst., Faculty Medicine, Kyushu Univ., Maidashi 3-1-1, Higashiku, Fukuoka 812, Japan) (Miyake, E.; Nomoto, K.; Takeya, K. *Acta Neuropathol (Berl)* 37(1): 27-29; 1977.

The cell surface antigens of cultured brain tumor cells were investigated using the mixed hemadsorption test with rabbit anti-human glioma serum (AGS). A strongly positive reaction to 800× AGS was observed in glioblastoma, astrocytoma, cerebellar astrocytoma, and fetal brain cells. A moderately positive reaction was obtained with three meningiomas, a metastatic brain tumor that originated from the lung, and HeLa cells. With skin or dural fibroblasts or kidney cells, no positive reaction was seen. It could not be determined whether the strongly positive reaction of fetal brain cells to AGS was due to a common antigen in the tumor and fetal cells; however, the antigenic differences between gliomas and neurinomas and fetal brain cells should be investigated further. (20 refs.)

77-0358 Colon Cancer-Associated Antigens in a Heterografted Human Tumor, GW-39. (Eng.) Goldenberg, D. M. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): p. 617-620; 1976.

A group of gastrointestinal tissue and oncofetal-associated antigens has been detected in GW-39 human colon tumors serially propagated in hamsters. The colon-specific antigens (CSA) have been classified as high molecular wt (HMW) and low molecular wt (LMW). HMW/CSA and LMW/CSA are gastrointestinal tissue-specific and tissue-associated antigens, respectively, as determined by immunodiffusion. CSAp, a protein-containing form, appears to be restricted to gastrointestinal tissues. CSAp, as determined by hemagglutination-inhibition, was higher in fetal gut and neoplastic colon tissue than in adult tissue. CSAp is water-soluble, has electrophoretic mobility of an α -globulin, and has a molecular wt of 100,000-150,000. CSAp appears to be increased in fetal gut and neoplastic colon tissues, and to have a greater gastrointestinal system specificity than other tumor-associated antigens described previously. CSAp may be a new marker for colon cancer. (10 refs.)

77-0359 In Vitro Inhibition of Lymphoproliferative Responses to Tumor Associated Antigens and of Lymphoma Cell Proliferation by Rat Splenic Macrophages. (Eng.) Oehler, J. R. (Lab. Immunodiagnosis, NCI, Building 1, Room 112, Bethesda, MD 20014) Campbell, D. A.; Herberman, R. B. *Cell Immunol* 28(2): 355-370; 1977.

The in vitro inhibition of lymphoproliferative responses to tumor-associated antigens and of lymphoma cell proliferation

by rat spleen cells was investigated. Inbred male W/Fu rats were inoculated sc with either 1×10^5 (C58NT)D Gross leukemia virus-induced tumor cells (regressor system) or French NTD tumor cells (a variant, progressor system). In a mixed lymphocyte tumor interaction (MLTI), suppressor cell activity was demonstrated in spleen cells from rats bearing the progressively growing lymphoma. Generation of a secondary cytotoxic response was also inhibited. Suppressor cell activity was also found to a lesser degree in spleens of rats that had rejected the C58NT(D) tumor. Pretreatment of progressor spleen cells with mitomycin C eliminated their ability to respond in MLTI, but had only a minor deleterious effect on suppressor cells. Passage of normal and immune spleen cells through a rayon column established that, after depletion of suppressor cells, the MLTI in the C58NT(D) system is still specific and dependent upon the presence of immune cells. In a growth inhibition assay (GIA), the progressor spleen cells had a dose-responsive inhibitory effect on the proliferation of C58NT(D) cells that corresponded with the degree of suppression observed in MLTI. In addition, normal spleen, but not thymus or lymph node, showed growth inhibitory activity. The kinetics of GI activity in spleen cells from animals injected with regressive or progressive tumors correlated well with tumor growth, indicating that GIA can be used for a suppressor cell assay. Characteristics of the effector cells indicated a macrophage-mediated effect. Lymphoproliferative responses to tumor-associated antigens in the rat could be substantially enhanced by removal of suppressor cells. (20 refs.)

77-0360 Resistance to Tumor Growth Mediated by *Listeria Monocytogenes*: Collaborative and Suppressive Macrophage-Lymphocyte Interactions In Vitro. (Eng.) Youdim, S. (Dept. Pathology, Univ. California San Diego, Sch. Medicine, La Jolla, CA 92037) Sharman, M. *J Immunol* 117(5): 1860-1865; 1976.

The resistance to tumor growth mediated by *Listeria monocytogenes* (LM) was studied. Immune spleen and peritoneal cells from C57BL/6 mice were separated into their adherent and nonadherent cellular components by adherence on plastic surfaces. Nonadherent cells were further treated with carbonyl iron powder to remove residual phagocytic cells. The dissociated cell populations were seeded on B-16 melanoma cells at a ratio of 300 effector cells to 1 tumor target cell. Neither the adherent nor the nonadherent cells alone demonstrated cytotoxicity either in the presence or absence of LM. However, recombination of these two cell components at a ratio of 100 adherent and 200 nonadherent cells to 1 target tumor cell reestablished this effect. A ratio of 200 spleen nonadherent cells and 100 adherent cells plus 2×10^5 LM and varying doses of 0.2×10^4 peritoneal macrophages per B-16 target cell was incubated with 100 precultured B-16 target cells, and the cytotoxic effect was determined at 72 hr. At ratios of 0-10 peritoneal macrophages: 1 B-16, only 5%-8% of the tumor cells survived the cytotoxic effect. With increasing numbers of peritoneal macrophages, increasing numbers of B-16 survived, indicating the blocking effect of

peritoneal macrophages on splenic T cell-adherent cell collaboration. Contrary to the inhibitory effects of peritoneal macrophages, splenic adherent cells collaborated with peritoneal T cells and had no blocking effect on synergism between peritoneal T cells and their complementary macrophages. The data show that LM immune T lymphocytes collaborate with macrophages or plastic adherent cells to inhibit the growth of B-16 melanoma in vitro. The interactions may also be suppressive or noncooperative, resulting in tumor cell proliferation. (40 refs.)

- 77-0361 Cellular and Humoral Response to Tumoral Antigens in the Hamster.** (Fre.) de Vaux Saint Cyr, C. (Institut de Recherches Scientifiques sur le Cancer, 94800 Villejuif, France) Loissillier, F.; Zuinghedau, J. *Ann Immunol (Paris)* 128C(1/2): 105-106; 1977.

Histological changes in the spleen and thymus and the immune response of the peritumoral region and serum were studied during the growth of a tumor induced by simian virus 40 (SV40) cells in Syrian hamsters. The hamsters were studied immunologically from the time of injection of SV40-transformed cells to a tumor growth of 4-7 g. The peritoneal reaction, characterized by plasmocytic cells containing intracytoplasmic immunoglobulin G (IgG) disappeared suddenly when the tumor was 4-6 g. Initially, the thymus increased in volume and cortex cells invaded the medullary area. When the peritumoral reaction ceased, thymus size diminished. At the time of max tumor growth, the spleen was invaded by plasmocytes containing IgG. The IgG had antibody function directed against the virus-induced antigens of the tumor cells. High levels of circulating antibodies were observed when the peritumoral reaction ceased and thymus size diminished. A final stage of the immune response was the pseudoleukemic-appearing invasion of the thymus and spleen with IgG-containing lymphoid cells. (no refs.)

- 77-0362 Cytotoxic Cell-Mediated Response to Tumor Antigens on Somatic Cell Hybrids.** (Eng.) Trinchieri, G. (Wistar Inst. Anatomy Biology, 36th St. at Spruce, Philadelphia, PA 19104) Aden, D. P.; Solter, D.; Knowles, B. B. *Transplant Proc* 9(1): 1161-1165; 1977.

The cytotoxic cell-mediated response to tumor antigens on somatic cell hybrids was examined. The hybrid lines were from human cells transformed by simian virus 40 (SV40) and normal peritoneal macrophages from inbred strains of mice. Immunization of mice with the hybrid cells resulted in the generation of cytotoxic effector T cells. Investigation of the kinetics of appearance of effector cells in the spleen after a single ip immunization with 3×10^7 cells demonstrated a peak of activity 8 days postinjection. The cytotoxic cells specifically lysed syngeneic hybrid cells containing the SV40 DNA integrated in the human chromosome and transformed syngeneic mouse cells. Hybrid cells with the SV40 genome integrated in the human chromosome 7 fully expressed SV40

tumor-associated specific antigen (TASA). This antigen was immunologically indistinguishable from that expressed by the transformed mouse cells, in which the SV40 DNA was integrated in the mouse genome. Cytotoxic spleen cells generated by immunization with hybrid cells were specific for SV40 TASA. It is concluded that human-mouse somatic cell hybrids can be used to detect and study the genetic control of human cell surface antigens. (9 refs.)

- 77-0363 Role of H-2 Histocompatibility on Generation of Cell-Mediated Cytotoxicity Against Virus-Induced Mammary Tumors in C3H Mice.** (Eng.) Stutman, O. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY) *Transplant Proc* 9(1): 1153-1155; 1977.

The effect of immunization of C3H and C3Hf mice with syngeneic and allogeneic mammary tumors (MT), induced by murine mammary tumor virus (MTV) on their ability to generate a cytotoxic response to syngeneic or allogeneic target cells was evaluated. The response of C3H (MTV+) and C3Hf (MTV-) animals immunized with syngeneic C3H tumors was determined. The MTV+ C3H mice had a vigorous response. When the C3H animals were immunized with allogeneic MT from a DBA/2, A, or RIII ($I \times C57BL/6$)F₁ origin, a vigorous response was generated against the syngeneic C3H target cells. The C3Hf (MTV-) animals showed no major differences when immunized with syngeneic or allogeneic MT. When immunized C3H or C3Hf (H-2 kk) mice were tested against allogeneic MT of a DBA/2 (H-2 dd) or RIII (H-2 rr) origin, the percentage cytotoxicity was generally lower than when tested in the syngeneic targets. The results suggest that the increased cytotoxic response observed in C3H (MTV+) mice after immunization with allogeneic MTV+ MT depends on recognition of both the MT virus and the H-2 antigens. (7 refs.)

- 77-0364 T-Cell-Mediated Concomitant Immunity to Syngeneic Tumors. I. Activated Macrophages as the Expressors of Nonspecific Immunity to Unrelated Tumors and Bacterial Parasites.** (Eng.) North, R. J. (Trudeau Inst., Incorporated, Saranac Lake, NY 12983) Kirstein, D. P. *J Exp Med* 145(2): 275-292; 1977.

AB6F₁ (A/J \times C57BL/6J) mice made T-cell-deficient by thymectomy and radiation, and protected with bone marrow cells, developed a much lower level of concomitant resistance than tumor-bearing (SAI sarcoma), irradiated control mice. In contrast to the strong resistance generated against a 10⁶ implant by tumor-bearing controls, T-cell-deficient mice displayed only marginal resistance to the growth of this size implant given on day 9 of primary tumor growth. The lymph node draining the site of the primary tumor in concomitantly immune donors contained T lymphocytes that by themselves could inhibit the growth of an implant of cells of the primary tumor in a normal recipient. The neutralization was specific for the homologous tumor. The host did not generate con-

comitant immunity after the implantation of SAI cells until after the latency period had ended. Immunity to a standard tumor cell challenge increased as the size of the primary tumor increased. Evidence that the lymph node cells responsible for tumor neutralization were T cells was supplied when it was observed that their capacity for neutralizing tumor growth, when present at a 50:1 ratio, was completely ablated by incubating them with anti- θ serum and complement. The growth of the sarcoma resulted in the generation of a state of resistance to growth of a second implant. The generation of immunity was associated with the generation of resistance to *Listeria monocytogenes*. T-cell-mediated concomitant immunity generated against a progressive SAI sarcoma shows striking similarities to T-cell mediated anti-bacterial immunity. In both cases, the generation of sensitized T cells in the presence of replicating antigen results in a systemic activation of macrophages that consequently results in a high level of nonspecific resistance to neoplastic cells and microbial parasites. (43 refs.)

77-0365 T-Lymphocyte Suppressor Activity in the Cytotoxic Response to the Teratocarcinoma 402AX of the Mouse. (Eng.) Isa, A. M. (Dept. Microbiology, Meharry Medical Coll., Nashville, TN) Sanders, B. R.; Parham, C. A. *Transplant Proc* 9(1): 1167-1169; 1977.

Mediation of the suppression of the immune response to mouse teratocarcinoma 402AX by suppressor cells having the properties of T lymphocytes was investigated. The cytotoxic cell to teratocarcinoma 402AX had the property of the macrophage. The cytotoxic activity of the macrophages increased with time following tumor implantation and reached a peak at 2 wk, but then declined. The cytotoxic activity by spleen cells reached a max at 2 wk of tumor growth and decreased by the third week. Selective elimination of θ -bearing lymphocytes by treating spleen cells with anti- θ alloantisera and complement caused an enhanced cytotoxic activity that reached peak levels 2 wk following tumor implantation. The effect was more pronounced in C57BL/6J mice, in which suppressor cell activity peaked at 1 wk of tumor implantation. Although a > 80% reduction in cytotoxic response was observed with spleen cells treated with ascitic fluid, no significant reduction was noted with spleen cells treated with irradiated tumor cells. The data suggest that suppressor cells have the properties of T lymphocytes. (9 refs.)

77-0366 Antigenic Specificity of the Cytolytic T Lymphocyte (CTL) Response to Murine Sarcoma Virus-Induced Tumors. I. Preferential Reactivity of In Vitro Generated Secondary CTL with Syngeneic Tumor Cells. (Eng.) Plata, F. (Laboratoire d'Immunologie des Tumeurs, Hôpital Gustave Roussy, Hôpital Cochin, F-75014 Paris, France) Jongeneel, V.; Cerottini, J. C.; Brunner, K. T. *Eur J Immunol* 6(11): 823-829; 1976.

The specificity of cytolytic T lymphocytes (CTL) formed in secondary mixed leukocyte-tumor cell cultures (MLTC) was investigated by using Moloney murine sarcoma virus (MSV)-immune spleen cells from mouse strains differing at the major histocompatibility complex (MHC) and tumor cells sharing the same MHC as each one of the responding lymphoid cell populations. When MSV-immune spleen cells from C57BL/6 (H-2b) and BALB/c (H-2d) mice were compared with respect to their ability to generate CTL in syngeneic secondary MLTC, both lymphoid cell populations were equally able to mount an anamnestic CTL response to MSV-associated antigens, as assessed by a short-term ^{51}Cr release assay. Quantitative analysis of the activity of both CTL populations on either H-2b or H-2d tumor cells indicated that target cells sharing the same MHC as the effector cells were lysed 10 to 100 times more efficiently than allogeneic target cells. Preferential lysis of syngeneic versus allogeneic tumor cells might be related to the establishment of effective adhesions between the former and CTL. Studies using MSV-immune spleen cells from congenic resistant mice gave evidence for the role of MHC in determining the antigenic specificity of CTL directed against MSV-associated antigens. Studies of the response of F_1 (H-2b/d) hybrid mice showed that stimulation of immune spleen cells with tumor cells from one parental strain or the other in secondary MLTC resulted in the generation of CTL capable of lysing tumor target cells of the same parental strain as the stimulating cells, but not of the other. The results suggest the presence of two sets of CTL precursor cells in F_1 MSV-immune spleens, each responding exclusively to tumor antigens associated with only one of the two parental phenotypes. (33 refs.)

77-0367 Nonspecific Activation of Murine Lymphocytes. I. Proliferation and Polyclonal Activation Induced by 2-Mercaptoethanol and α -Thioglycerol. (Eng.) Goodman, M. G. (Scripps Clinic and Res. Foundation, Dept. Immunopathology, LaJolla, CA 92037) Weigle, W. O. *J Exp Med* 145(3): 473-489; 1977.

Spleen cells from C3H mice were cultured and tested for the effect of 2-mercaptoethanol (2-ME) and α -thioglycerol (α -TG) on proliferation and polyclonal activation. A highly significant uptake and incorporation of ^3H -thymidine into DNA and in morphological blast transformation were observed at an optimal concentration of $5 \times 10^{-3}\text{M}$ for both compounds, either in serum-containing or serum-free media. These observations were dose-dependent. The kinetic peak of these responses occurred at day 3 of culture. A proliferative response was seen in spleen cell cultures from nu/nu mice with 2-ME; however, it was somewhat lower than the response of nu/+ littermates. Cultures of B-lymphocytes incorporated ^3H -thymidine to a degree at least equal to that of normal spleen cell cultures. T cells did not respond to 2-ME, α -TG, or concanavalin A in the absence of serum, however, with 5% fetal calf serum, T-cell responses (always of a lower magnitude than B-cell responses) occurred. When B and T cells were cocultured, a synergistic effect was noted. There was minimal macrophage dependency of the 2-ME and α -TG effect. A

greater effectiveness was seen with α TG relative to 2-ME, which may be due to its chemical structure. These compounds may have value in the study of lymphocyte activation. (39 refs.)

- 77-0368 Total T Lymphocytes in Primary Bronchial Carcinoma.** (Eng.) Roberts, H. L. (Dept. Medicine, Univ. Liverpool, Liverpool, L69 3BX, England) Donohoe, W. T.; Hewitt, S.; Price Evans, D. A. *Thorax* 32(1): 84-87; 1977.

The levels of circulating total lymphocytes and T-cell lymphocytes were determined in the following groups of people: A, nine healthy adults; B, 19 age-matched control patients with benign disease (hernia, cholelithiasis, diverticulosis coli); C, 23 patients with localized bronchial carcinoma (BC); D, 25 patients with metastatic BC; and E, 20 patients who had been given postoperative immunotherapy after complete resection of BC. Absolute lymphocyte counts in Groups A-E were: 2,253, 2,214, 2,411, 1,461, and 2,426, respectively. T-cell counts for Groups A-E were: 1,478, 1,496, 1,624, 970 and 1,674, respectively. The mean percentages of lymphocytes that were T cells in Groups A-E were: 66.8, 68.2, 66.7, 64.4, and 67.1, respectively. Thus, there was no significant difference in the mean percentage of T cells between the groups and no evidence of T-cell deficiency in early BC. Lymphopenia was a feature of BC patients with metastatic disease. (17 refs.)

- 77-0369 Establishment of Peripheral Lymphoid Cell Cultures from Patients with Hodgkin's Disease Depending on Epstein-Barr-Virus-Reactivity and Cellular Immunity.** (Eng.) Diehl, V. (Hamatologie-Onkologie, Medizinische Hochschule, Karl-Wiechert-Allee 9, 3000 Hannover, W. Germany) Johansson, B. *Blut* 34(3): 227-236; 1977.

Long-term cultures of the peripheral blood lymphocytes from 43 patients with Hodgkin's disease were studied for signs of spontaneous growth. Establishment of these cultures was found to depend on a positive Epstein-Barr Virus (EBV) seroreactivity and intact delayed hypersensitivity to tuberculin. The overall establishment rate was 18/60 attempts: 16/34 in the patient group who received no treatment 1 mo prior to testing and 2/26 in the patients who were treated with either radiotherapy or cytostatic drugs and/or corticosteroids. Advanced disease correlated inversely to the establishment of cell lines. Out of 49 attempts, no cultures could be established from umbilical cord blood. Cultures of peripheral blood cells from healthy individuals were successful in only 12/66, even though all these donors were EBV-positive and 86% were reactive to tuberculin. With the assumption that stimulation by a specific antigen in combination with the presence of EBV is necessary for continuous growth in vitro, it is suggested that stimulation may have occurred in vivo in the Hodgkin's disease patients. The establishment of cultures may therefore be due to an immunological reaction in vivo, followed by

EBV transformation, although the nature of the tumor antigen remains unclear and is still speculative. (30 refs.)

- 77-0370 Lymphocyte Responses to EBV-associated Antigens in Infectious Mononucleosis, and Hodgkin's and Non-Hodgkin's Lymphoma Patients, with the Leukocyte Adherence Inhibition Assay.** (Eng.) Chan, S. H. (NCI, NIH, Bethesda, MD) Wallen, W. C.; Levine, P. H.; Periman, P.; Perlin, E. *Int J Cancer* 19(3): 356-363; 1977.

The leukocyte adherence inhibition (LAI) assay was used as a test for cellular immunity to Epstein-Barr virus (EBV) antigens in 84 subjects without cancer, 101 carcinoma patients, 47 patients with lymphoma, and 22 patients with infectious mononucleosis (IM). The response to EB soluble antigen and EB virion antigen was followed. The response to the soluble antigen was delayed in IM patients, but that to the virion antigen was present at the time of diagnosis. The patients with Hodgkin's disease had decreased responses to the EBV-associated soluble antigen. An elevated cell-mediated immune response to virion antigen was observed in patients with non-Hodgkin's lymphoma, Hodgkin's disease, and IM. In comparing the LAI reactivity to EBV titers in the lymphoma patients, it was found that Hodgkin's disease patients with high titers were less often reactive to soluble antigen in the assay than non-Hodgkin's lymphoma patients. The increased cell-mediated immune response to virion antigen in Hodgkin's disease patients requires a reevaluation of the suggestion that the high EBV titers in this disease are solely a result of decreased cellular immunity. (24 refs.)

- 77-0371 Blood B and T Lymphocytes and In Vitro Cellular Immune Reactivity in Untreated Human Malignant Lymphomas and Other Malignant Tumors.** (Eng.) Heier, H. E. (Lab. Haematology and Lymphology, Norwegian Radium Hosp., Montebello, Oslo 3, Norway) Klepp, R.; Gundersen, S.; Godal, T. *Scand J Haematol* 18(2): 137-148; 1977.

The in vitro activity of peripheral blood lymphocytes was examined prior to treatment in 18 patients with Hodgkin's disease, 11 with lymphosarcoma, 13 with reticulosarcoma, 20 with various solid tumors, and in 37 normal controls. The results showed that with the exception of the lymphosarcoma group, all patient group mean values were significantly lower than that of controls. In the Hodgkin's disease and solid tumor groups, the patients with disseminated disease had somewhat lower mean values than those with localized disease. The T-lymphocyte mean value for all patients was $> 50\%$, but the value for B lymphocytes did not exceed 20%. The total number of T cells was reduced to a statistically significant level in the Hodgkin's disease and reticulosarcoma groups ($p < 0.01$) compared to controls. In the Hodgkin's disease, reticulosarcoma, and solid tumor groups, the max phytohemagglutinin (PHA) response tended to be initiated by a higher concentration of the mitogen than in the control

and lymphosarcoma groups. For all patients, the reactivity was lower than the stimulating activity in mixed lymphocyte culture. These results indicate that immunological changes occur prior to treatment in association with various neoplastic and malignant disease states. (38 refs.)

77-0372 T and B Lymphocytes in Malignant Melanoma Patients. (Eng.) Babusikova, O. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) Novotna, L.; Schnekova, K.; Turkova, D.; Havranova, M. *Neoplasma* 23: 635-644; 1976.

Cellular immunocompetence was evaluated in 64 patients with malignant melanoma and in 33 control donors. The percentages of T and B lymphocytes were determined in vitro by the E and EAC rosette methods, respectively, using 2×10^6 cells/ml, and lymphocyte survival was tested in short-term cultures (1×10^6 cells/ml) with the mitogen phytohemagglutinin (PHA). All patients were tested before treatment; 20 of them were tested at 6- to 8-wk intervals after treatment with surgery and postoperative ^{60}Co contact therapy (total dose, 5,000-6,000 R). In the patients, the percentage of T cells was lower than in controls; this decrease could be correlated with the stage of the disease, the greatest decline occurring in the dissemination stage. Concomitantly, there was a corresponding increase in both B lymphocytes and null (nonrosetting) cells. Lymphocytes from patients with tumors with a presumed deficiency of T cells survived better with a standard PHA dose than cells from healthy donors. In postoperative patients, normal T and B lymphocyte values seemed to be indicative of remission, and low proportions of T cells reflected tumor progress. Thus, follow-up of immunocompetence in melanoma patients may indicate response to therapy or relapse. (43 refs.)

77-0373 Role of H-2 Region in Cytolysis of Virally Induced Lymphoma Cells by T Lymphocytes. (Fre.) Gomard, E. (Laboratoire d'Immunologie et de Virologie des Tumeurs (INSERM U 152), Hopital Cochin, 75014 Paris, France) Duprez, V.; Levy, J. P. *Ann Immunol (Paris)* 128(1/2): 7-9; 1977.

Previous experiments have shown that the cytolysis of viral-induced lymphoma cells by anti-Moloney sarcoma virus (MSV) T lymphocytes requires an H-2 identity on the T lymphocytes and target cells. Anti-MSV T lymphocytes from mice with various gene recombinations in the H-2 region were tested against target cells H-2a, d, or b, to clarify the role of the H-2 subregions in the immune response. The H-2a and d target cells were lysed by T lymphocytes having the antigens D or K + I-A; the H-2b target cells were lysed only by T lymphocytes bearing the D antigen. The Ia antigen does not appear to be a factor in the interaction of lymphoma cells and anti-MSV T lymphocytes. The experiments suggest that the I antigen of the Ir gene controls the formation of the anti-H-2, murine leukemia virus T lymphocyte. (4 refs.)

77-0374 Gross-Virus-induced Lymphoma in the Rat. V. Natural Cytotoxic Cells are Non-T Cells. (Eng.) Shellam, G. R. (Immunology Branch DCBD, NCI, NIH, Bethesda, MD 20014) *Int J Cancer* 19(2): 225-235; 1977.

A further characterization of the natural killer (NK) cells of rats is presented. Analysis of cell size by velocity sedimentation at unit gravity showed an enrichment of both NK cells and cytotoxic T cells at 4-5 mm/hr. Cytotoxic cells exhibited an additional peak at 7-8 mm/hr. NK cells were found to be heat-labile, losing all activity after several hours at 37 C. Cytotoxic T cells were stable at 37 C. Sensitivity to ionizing radiation was analyzed by irradiation with ^{60}Co at 18 rads/min and assay by the chromium-release test (CRT). NK cells demonstrated a biphasic sensitivity to gamma radiation, losing 50% of their activity after 1,000 rads but maintaining some activity after 5,000 rads. Cytotoxic T cells lost all cytotoxicity after 5,000 rads. Divalent calcium ions were required by both NK cells and cytotoxic T cells for cytotoxicity. The use of cell surface markers revealed that NK cells are non-phagocytic, non-T cells that lack surface immunoglobulin and Fc receptors. Cytotoxicity tests following treatment of the NK cells with papain indicate that arming antibodies are not passively acquired by NK cells. (30 refs.)

77-0375 Expression of Human B-Lymphocyte Antigens by Most Lymphocytic and Myelocytic Leukemia Cells. (Eng.) Billing, R. J. (Dept. Surgery, Sch. Medicine, Univ. California, Los Angeles, CA 90024) Ting, A.; Terasaki, P. I. *Transplant Proc* 9(1): 1145-1147; 1977.

The expression by myelocytic and lymphocytic leukemia cells of human B-lymphocyte antigens was studied. Twenty-eight human anti-B-cell alloantisera and 3 rabbit anti-B-cell antisera were tested by complement-dependent cytotoxicity against human leukemia cells. The same cells that reacted with the human alloantisera also reacted with the three rabbit antisera. Two groups of leukemia cells could be identified on the basis of this reactivity: a positive group consisting of 19 acute myeloblastic leukemia (AML), 14 acute lymphoblastic leukemia (ALL), 8 chronic myeloblastic leukemia (CML), and 7 chronic lymphocytic leukemia types and a negative group of 6 AML, 5 ALL, and 2 CML types. The rabbit sera reacted against all the cells in the positive group, but each of the human sera reacted with only some of these cells. The pattern of reactivity of the human sera suggested that they were directed against a polymorphic system of antigen. From their reactions against normal B lymphocytes, five alloantigenic B-cell specificities (Groups B1-B5) were obtained. The most significant finding was that Group B2, which was present on 23% of a panel of B lymphocyte from 105 normal donors, was not present on any of the tested leukemia cells from 60 different patients. Group B1 was present on 48% of normal lymphocytes but on only 18% of the leukemia cells. The specificities of Groups B3, B4, and B5 were not significantly different on both cell groups. Group B2 was also absent from cultured lymphoblastoid cell lines. Not only leukemia cells of the lymphocytic subclasses but also most of

those of the myeloid subclasses express B-lymphocyte alloantigens. (7 refs.)

- 77-0376 Reactivity of Alloantibodies of the Merrit B-Cell System with Leukemic Cells and Lymphoblastoid Cell Lines.** (Eng.) Naeim, F. (Dept. Pathology, UCLA Sch. Medicine, Los Angeles, CA 90024) Leibold, W.; Gatti, R.; Walford, R. L. *Transplant Proc [Suppl]* 9(1): 151-155; 1977.

Thirty-eight sera containing Merrit alloantibodies were tested against 20 lymphoblastoid cell lines, 12 HLA-D-homozygous and 8 HLA-D-heterozygous, and the reactivity patterns were compared with those of a panel of 20 chronic lymphatic leukemia (CLL) cells. Unlike CLL cells, the lymphoid cell lines frequently showed positive cytotoxic reactions only with certain sera of a particular Merrit group, and they were consistently negative with other sera of that group. To investigate the possibility of a cytotoxicity-negative absorption-positive (CYNAP) phenomenon involving the cell lines, a series of absorption and back-testing studies was made with three sera containing Merrit alloantibodies: JH, Evans, and F42. Sera Evans and F42 were absorbed with selected normal peripheral lymphocytes to delete anti-HLA activity. JH showed no anti-HLA activity in cytotoxic tests against normal cells. Twelve of the lymphoblastoid lines were HLA-D-homozygous. Each cell line displayed positive reactions for no more than 2/13 Merrit groups, and 4/8 heterozygous lines were positive for 3/13 groups. The lymphoblastoid lines demonstrated a higher incidence of the CYNAP phenomenon than CLL cells. The Merrit system is linked with the HLA supergene region. (16 refs.)

- 77-0377 Reactivity of the Merrit B-Cell Alloantisera with Hairy Cells (Letter to Editor).** (Eng.) Naeim, F. (Univ. California Medical Center, Los Angeles, CA 90024) Gossett, T.; Walford, R. L. *N Engl J Med* 296(15): 882; 1977.

Peripheral mononuclear cells were obtained from 10 patients with hairy-cell leukemia. In complement-dependent microcytotoxicity tests, these cells showed positive reactions with several Merrit B-cell alloantisera. Human antisera were obtained from multiparous women and from patients after renal-graft rejection and planned immunization. The antigens were segregated in family studies with HLA, but were distinct from HLA-A, HLA-B, and HLA-C antigens. Some B-cell antigens were closely associated with or identical to HLA-D

determinants. The presence of B-cell markers on these cells and the reactivity of B-cell alloantibodies with hairy cells support the B-lymphocyte origin of hairy cells. (6 refs.)

- 77-0378 B-Lymphocyte Alloantigens Extracted from CLL Cells.** (Eng.) Watson, R. D. (Dept. Surgery, Univ. Toronto, Toronto, Ontario, Canada) Falk, J. A.; Falk, R. E. *Transplant Proc* 9(1): 161-164; 1977.

The B-lymphocyte alloantigens extracted from chronic lymphocytic leukemia (CLL) cells were assessed. A pregnant serum (West) with antibody against the HLA-A2 and A2 antigen specificities was cytotoxic to the peripheral blood mononuclear cells (PBL) from 5/6 CLL patients tested initially, including two HLA-A2-negative patients. The PBL from one of these patients (CLL-M) were used. The cytotoxicity of whole West serum for CLL-M cells was not removed by absorption with HLA-A2 spleen cells. Absorption with CLL-M cells removed the cytotoxicity. B-lymphocyte-enriched, T-lymphocyte-enriched, and whole lymphocyte populations from the HLA-A2 PBL donor were tested against whole West serum, West serum absorbed with HLA-A2 spleen cells, and West serum absorbed with HLA-A2 spleen cells and CLL-M cells. There was similar cytotoxicity of whole West serum against all three sets of cells. There was < 15% cytotoxicity of the T-cell-enriched and whole lymphocyte populations by the A-2 absorbed West serum and 55% cytotoxicity of the B-cell-enriched population. There was a broad peak of antigen in the high molecular weight (MW) fractions and a narrow peak of antigen at 60,000 MW using Ultrogel AcA 34. It may be possible to purify human immune-associated antigens by methods that retain biologic activity. (8 refs.)

See also:

- *(Rev.): 77-0001, 77-0033, 77-0046, 77-0048, 77-0051, 77-0052, 77-0053, 77-0060, 77-0062, 77-0063, 77-0064, 77-0065, 77-0066, 77-0067, 77-0068, 77-0069, 77-0070, 77-0071, 77-0072, 77-0073, 77-0074, 77-0075, 77-0076, 77-0080, 77-0095, 77-0104, 77-0111, 77-0115.
*(Chem.): 77-0146, 77-0151, 77-0152, 77-0161.
*(Viral): 77-0222, 77-0223, 77-0231, 77-0232, 77-0237, 77-0239, 77-0241, 77-0252, 77-0257, 77-0274, 77-0277, 77-0278.
*(Path.): 77-0379, 77-0380, 77-0385, 77-0386, 77-0400, 77-0402, 77-0411, 77-0423, 77-0429, 77-0432, 77-0457, 77-0458, 77-0475, 77-0477, 77-0513, 77-0519, 77-0520.

PATHOGENESIS

7-0379 **Ecotaxis: The Principle and Its Application to the Study of Hodgkin's Disease.** (Eng.) De Sousa, M. (Lab. Cell Ecology, Sloan-Kettering Inst. for Cancer Res., 1275 York Ave., New York, NY 10021) Yang, M.; Lopes-Corrales, E.; Tan, C.; Hansen, J. A.; Dupont, B.; Good, R. A. *Clin Exp Immunol* 27(1): 143-151; 1977.

The distribution of T and B cells in the spleen, blood, liver, and involved and uninvolved lymph nodes of five children with Hodgkin's disease was studied. Low percentages of T cells in peripheral blood were found in three patients (aged 5, 15, and 10 yr) in Stages IA (23.5%), IIA (45.5%), and IIIB (62.5%), respectively. The other two patients (aged 7 and 8 yr), in Stage IIIB, had normal percentages. The proportions of T cells in the spleens of the three patients with low peripheral blood T cells were higher (61%, 51%, and 83%). A considerable proportion of the lymphoid cells in the blood of these three could not be characterized by any of the surface markers utilized. In all five children, the proportions of EAC rosette and surface immunoglobulin-bearing cells were consistently high in the spleen. The in vitro response to stimulation with nonspecific mitogens was investigated. Phytohemagglutinin (PHA) was the one that differed most from the control dose-response curve, either by being lower than the control at all six mitogen concentrations tested, or at the two lower concentrations. The effect of splenectomy was examined in one patient who was diagnosed as Stage IA and who had received radiotherapy (4,000 rads) confined to a small area of the right cervical region. The peripheral blood lymphocyte count at presentation was $1,072/\text{mm}^3$. It increased to $2,550/\text{mm}^3$ 3 mo after splenectomy. The percentage of peripheral blood T cells increased from 23.5% to 43.5%, and the patterns of the responses to PHA and concanavalin A were nearer the control range than the ones observed prior to splenectomy. Nevertheless, the response at the low concentrations of PHA was still abnormal. It is concluded that lymphocyte depletion from one compartment of the lymphoid system (ie, the peripheral blood or some involved lymph nodes) does not necessarily reflect an absolute decrease of circulating lymphocytes. (27 refs.)

7-0380 **Hodgkin's Disease in Siblings: A Family Study.** (Eng.) Perlin, E. (Natl. Naval Medical Center, NCI, Bethesda, MD 20014) Levine, P. H.; McCoy, J.; Dean, J.; Herberman, R. *Oncology* 33(3): 116-118; 1976.

A large family in which two siblings were documented to have the nodular sclerosis type of Hodgkin's disease (HD) was evaluated for immunological competency, distribution of HL-A antigens, and Epstein-Barr virus (EBV) antibody titers. The siblings involved were a Caucasian girl and her older brother, who were 16 and 22 yr old, respectively, at the time of diagnosis; only the brother is now living in complete remis-

sion. In all of the eight family members examined, the HL-A antigens frequently associated with HD were not found, and normal immunoglobulin levels were obtained. The brother with HD showed impaired cellular immunity by delayed cutaneous hypersensitivity (DCH) skin testing and mitogen (phytohemagglutinin) stimulation of his peripheral lymphocytes, when tested after receiving radiation therapy; however, he had a normal DCH when retested at a later date. Antibody titers to the viral capsid antigen of EBV were in the high normal range in the HD patient and one male sibling. The lack of genetic markers in this family indicates that environmental factors may play a large role in the pathogenesis of nodular sclerosing HD. (22 refs.)

77-0381 **Infectious Mononucleosis in Hodgkin's Disease. A Further Case Report.** (Eng.) Davidson, R. J. (Haematology Unit, Dept. Pathology, Univ. Medical Buildings, Foresterhill, Aberdeen AB9 2ZD, Scotland) *Acta Haematol (Basel)* 57(3): 152-155; 1977.

A case of infectious mononucleosis (IM) in Hodgkin's disease (HD) is reported. In June 1966, a 24-yr-old woman presented with painless cervical lymph node enlargement involving the left posterior triangle. The affected nodes were excised, and their histology indicated a chronic granulomatous reaction that was regarded as tuberculous, although an atypical HD was not excluded. A few months later, an unproductive cough prompted an x-ray exam that disclosed opacities in the right hilar and left mid-zones, with a sympathetic effusion at the left base. Enlarged lymph nodes from the right anterior cervical chain were excised in December 1968, and a diagnosis of HD was established. The histology was of a lymphocyte-depleted type, with necrosis as a prominent feature. The patient was started on nitrogen mustard and steroid therapy. In March 1969, she was readmitted complaining of nausea and vomiting of 5 days' duration. A diagnosis of IM was confirmed by the finding of a positive IM slide screening test (Monospot), a diagnostic differential absorption titer of 1:256 following guinea pig kidney absorption, and an Epstein-Barr virus antibody titer of 1:160. Following recovery from this intercurrent illness, the patient's HD continued to progress, and in April 1970, she died from septicemia while receiving intensive cytotoxic therapy. The pathological profile does not support the concept of a causal relationship between HD and Epstein-Barr virus. (16 refs.)

77-0382 **Neurologic Complications of Hodgkin's Disease. Choroid Plexus Involvement.** (Eng.) Sanchez, J. E. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD 21201) Garcia, J. H.; Kwee, H. *Acta Neuropath (Berl)* 37(2): 169-171; 1977.

The case of a 49-yr-old man who developed, shortly before death, neurologic symptoms seemingly related to extensive involvement of the choroid plexus and surrounding structures by lymphoma (Hodgkin's) is presented. The patient was diagnosed as having Hodgkin's disease (inguinal lymph nodes) in April 1967. On admission in August 1974, he was oriented but unable to recall earlier events. There was a left-sided trigeminal deficit and left deviation of the tongue. Cytologic evaluation of the cerebrospinal fluid demonstrated malignant lymphoma cells. In October 1974, he developed numbness of the trunk and legs. Following radiotherapy and steroids, there was complete resolution of the intraspinal block. Shortly thereafter, the patient had progressive weakness, lassitude, and obtundation, and he expired. Pertinent autopsy findings included cachexia, numerous decubitus cutaneous ulcers, and enlargement of several lymph nodes, the liver, and spleen. The external surface of the cerebrum was unremarkable. On coronal sections, there were numerous areas of softening and hemorrhage involving the choroid plexus and the neighboring structures in the lateral ventricles, third and fourth ventricles, and the adjacent white matter. Light microscopy findings are also reported. Involvement of the choroid plexus is a complication of lymphoma (Hodgkin's). (10 refs.)

77-0383 An Ultrastructural Analysis of Lymphoreticular Cell Interactions in Primary Cultures of Human Non-lymphoid Neoplasms and Lymphomas. (Eng.) Underwood, J. C. (Dept. Pathology, Univ. Sheffield Medical Sch., Sheffield S10 2RX, England) *J Pathol* 120(2): 75-82; 1976.

Lymphoreticular cell interactions in primary cultures of human lymphomas and nonlymphoid neoplasms were analyzed ultrastructurally. Most of the lymphoreticular cells in cultures of the 14 nonlymphoid neoplasms (4 malignant melanomas, 3 squamous carcinomas of lung, 2 renal cell carcinomas, 1 seminoma, 1 squamous carcinoma of penis, 1 adenocarcinoma of rectum, 1 adenocarcinoma of breast, and 1 fibrous histiocytoma) were lymphocytes and macrophages. In some cultures, the lymphoreticular cells outnumbered the tumor cells. Macrophages varied significantly in size, shape, and structure, making their identity uncertain upon phase-contrast microscopy alone. Many were disk-shaped and slightly protuberant, with numerous hairlike processes radiating from their periphery. Sustained contact between macrophages and lymphocytes was extremely frequent. Several lymphocytes were often seen on the surface of a single macrophage. Fusion of macrophages by interdigitation of filiform processes to form giant cells occurred in one culture, a squamous carcinoma of the penis. Giant cells were present in the stroma of the original tumor tissue. Close contact between tumor cells and macrophages was also common. Nine lymphomas (4 Hodgkin's lymphomas, 3 reticulum cell sarcomas, and 2 lymphosarcomas) were also examined. In Hodgkin's lymphoma, lymphocytes and macrophages were numerous. A third cell type was large and flat, with an angular profile. Large round cells with a markedly bilobed nucleus reminis-

cent of Reed-Sternberg cells were also identified. Cellular interactions were observed with increasing frequency after 3-days of in vitro cultivation. Lymphocytes showed a significant tendency to cluster around other cells, notably giant cells and macrophages. There was a close spatial relationship between lymphocytes and degenerate macrophages. Two of the reticulum cell sarcoma biopsies demonstrated effacement of nodal architecture by abnormal cells with histiocytic features. The third showed an almost pure population of abnormal reticulum cells. The cultural characteristics of one lymphosarcoma were similar to those of Hodgkin's disease. The other showed a typical diffuse pattern, with large pale cells interspersed among sheets of small lymphocytes. (22 refs.)

77-0384 Burkitt's Lymphoma Cell Leukemia. (Eng.) Acar, S. (Hacettepe Univ. Faculty Medicine, Dept. Pediatrics, Ankara, Turkey) Tekinalp, G.; Ozsoylu, S.; Cevik, N.; Yasar, H. *Acta Haematol (Basel)* 57(3): 188-192; 1977.

The occurrence of Burkitt's lymphoma cell leukemia in a 5-yr-old boy is reported. The patient was admitted with complaints of paleness, loss of appetite, pain and swelling of the legs, weakness, and rapid enlargement of the abdomen of 10 days' duration. Physical examination demonstrated an acutely sick-looking, pale boy with edema of legs and eyelids. Several lymph nodes in the cervical, axillary, and inguinal regions were enlarged ($1 \times 1 \times 1.5$ cm). The liver and spleen were 7 and 2 cm palpable below the costal margins, and the collateral veins over the abdomen were prominent. The cellular bone marrow was replaced completely by multiple, vacuolated Burkitt's lymphoma cells that had a basophilic cytoplasm and a finely granular nuclear chromatin with one to five nucleoli. Hypoproteinemia and hyperuricemia were documented. With the diagnosis of acute leukemia, the patient was given vincristine (2 mg/meter²/day, po), methotrexate (12 mg/m²/wk, intrathecally), and prednisolone (120 mg/m²/day, po). On the third week of admission, he was given penicillin ($8 \times 300,000$ units, iv) and gentamicin (3 mg/kg/day) because of bronchopneumonia. The infection did not respond to therapy, and the patient died 4 days later. Only eight cases of Burkitt's lymphoma cell leukemia have been diagnosed while the patient was alive. (22 refs.)

77-0385 Lymphocytic Lymphoma of Mediastinal Localization Following Immunosuppressive Therapy. (Hun.) Sonkodi, S. (Szegedi Orvostudományi Egyetem I. and II. sz. Belklinika, Szeged, Hungary) Vigh, E.; Kovacs, A.; Tiszai, A. *Magy Onkol* 20(3): 197-200; 1976.

The case history of an 18-yr-old patient with mediastinal lymphocytic lymphoma is presented. The patient had been treated with immunosuppressive therapy for the nephrotic syndrome between 5 and 14 yr of age. It is suggested that the immunosuppressive therapy caused the malignant lymphoma. The literature is reviewed. (23 refs.)

77-0386 The Mutual Clonal Origin of the Lymphoplasmocytic and Lymphoma Cell in Alpha-Heavy Chain Disease. (Eng.) Ramot, B. (Inst. Hematology, Chaim Sheba Medical Center, Tel-Hashomer, Israel) Levanon, M.; Hahn, Y.; Lahat, N.; Moroz, C. *Clin Exp Immunol* 27(3): 440-445; 1977.

Biosynthetic studies were conducted on a tumor of the intestine and a mesenteric lymph node tumor obtained from a 37-yr-old man with α -heavy chain disease (α -HCD). The results showed that both tumors synthesized α -HCs; however, the intestinal tumor cells synthesized and actively secrete α -HC during the first 2.5 hr of incubation, but the lymph node tumor cells synthesized α -HCs that were shed into the culture medium only after 20 hr. These chains were located on the surface of the immunoblastic tumor cells. In both tumors, the molecular size of the α -HC was smaller than the α -HC obtained from myeloma protein. It is suggested that the proliferating plasmocytes and the immunoblastic tumor cells originate from the same defective clone. (13 refs.)

77-0387 Hand-Mirror-Cell Leukaemia (Letter to Editor). (Eng.) Schumacher, H. R. (Div. Hematopathology, Dept. Lab. Medicine, Natl. Naval Medical Center, Bethesda, MD 20014) Perlin, E.; Miller, W. M.; Stass, S. A. *Lancet* 1(8012): 655-656; 1977.

A variant of acute lymphoblastic leukemia, which was characterized by numerous hand-mirror-type lymphocytic-lymphoblastic cells in the bone marrow, a marked resistance to chemotherapy, a prolonged survival without treatment despite morphological evidence of active disease), and normal platelet counts, occurred in a 22-yr-old woman. Three additional cases (all in women) have been reported in the literature. Further observations are needed to determine the frequency, possible specificity, and diagnostic, prognostic, and therapeutic implications of this morphological finding. (2 refs.)

77-0388 Surface Features of Sezary Cells: A Scanning Electron Microscopy Study of 5 Cases. (Eng.) Polliack, A. (Dept. Haematology, Hadassah Univ. Hosp., Jerusalem, Israel) Djaldetti, M.; Reyes, F.; Biberfeld, P.; Daniel, M. T.; Flandrin, G. *Scand J Haematol* 18(3): 207-213; 1977.

The surface features of circulating cells from five patients with typical Sezary's syndrome (SS) were assessed by scanning electron microscopy. In all cases, including samples in which cells were fixed and prepared by different methods, the same surface features were observed. Like the lymphocytes isolated from patients with chronic lymphocytic leukemia (CLL), most SS cells were spherical, with varying numbers of short, fingerlike microvilli. Most often, the cells had moderate to significantly villous surfaces and they did not display ruffled membranes. Other villous cells were more irregular,

demonstrating clusters of microvilli polarized to one area of the cell surface. Other cells had extensions of cytoplasm bearing microvilli, which resembled small underdeveloped uropods. A small proportion of cells, not exceeding 30%, was smaller in size and demonstrated few microvilli. Most SS cells cannot be distinguished from CLL cells on the basis of their surface architecture under the scanning electron microscope. (33 refs.)

77-0389 Hairy-Cell Leukaemia [Letter to Editor]. (Eng.) Golomb, H. M. (Section Hematology/Oncology, Dept. Medicine, Univ. Chicago, Chicago, IL 60637) *Lancet* 1(8007): 372-373; 1977.

In previous letters on the scanning electron microscopy (SEM) of cells in leukemic reticuloendotheliosis (hairy-cell leukemia) and chronic lymphocytic leukemia, the appearances reported have differed depending on whether spleen cells, peripheral blood, or lymph nodes were studied and on the method of preparation. Because of these differences, hairy cells from several sites, and prepared by slightly different methods, were examined in two patients. The first was a 45-yr-old man with a WBC count of 7,900/ μ l and with 48% hairy cells. The second patient was a 65-yr-old man with a WBC count of 8,900/ μ l and with 12% hairy cells. The surface ultrastructure in the first patient was almost the same for cells taken from the peripheral blood or spleen and prepared in the same way through Ficoll-Hypaque gradient centrifugation and when they were taken from the same site (the spleen) and prepared either as a suspension or fixed as whole tissue. The surface projections appeared to be slightly more spiked in the peripheral blood preparations, but the broad-based, exaggerated ruffles in association with an occasional patch of microvilli were presented in all four samples. The spiked appearance of the projections could possibly account for the hairy appearance in smears of peripheral blood cells, in contrast to the irregular pseudopodal appearance in smears of bone marrow cells. Cells prepared in the same way from the second patient were similar to each other and to the cells from the first patient. Although there may be subtle differences depending on cell site, the striking differences previously reported cannot be supported. (6 refs.)

77-0390 Further Ultrastructural Characterization of Hairy Cells of Leukemic Reticuloendotheliosis. (Eng.) Katayama, I. (Dept. Pathology, Univ. Massachusetts Medical Center, 55 Lake Ave. North, Worcester, MA 01605) *Am J Pathol* 86(1): 163-184; 1977.

Hairy cells of leukemic reticuloendotheliosis (LRE) were characterized ultrastructurally by the transmission and scanning electron microscopes. The surface of the LRE cells was covered by two types of cytoplasmic projections: slender fingerlike processes (microvilli) measuring 50-150 millimicrons in diameter and 0.6-1.4 μ m in length and broad-based tongue-like processes (pseudopods) measuring approx 1 μ m in width

and 3 μm in length. A ribosome-lamella complex (RLC) was observed in specimens from 10/23 patients with LRE. In these 10 patients, the RLC was found in from 0.2% to 90% of the LRE cells. In the spleen, great numbers of LRE cells were noted in the cords and sinuses. The ultrastructure of LRE cells was the same in the spleen as in the blood. Their cytoplasmic projections interdigitated among themselves or often encircled RBC, platelets, or segments of basal lamina. Two of nine spleens suggested erythrophagocytosis by LRE cells because of the presence of RBC deep in their cytoplasm. The leukemic lymphocytes in lymphosarcoma cell leukemia and chronic lymphocytic leukemia (CLL) showed the same spectrum of morphology as in normal lymphocytes, ranging from mature small lymphocytes to blast forms. When compared with LRE cells, these lymphocytes demonstrated a larger nucleocytoplasmic ratio, fewer nuclear indentations, fewer and shorter microvilli, and no pseudopods. RLC's were found in 2/20 patients. Although > 1,000 lymphocytes were screened in both patients, RLC's were noted in only one lymphocyte in the blood of a CLL patient and in two lymphocytes in the spleen of a patient with lymphosarcoma cell leukemia. Lymphocytes from healthy individuals and CLL patients measured 4.8 μm in av diameter. Most lymphocytes demonstrated short, stublike microvilli, usually < 0.5 μm in length. LRE cells in immediately fixed blood from LRE patients measured 5.8 μm in av diameter. In addition to the LRE cells, these blood samples usually contained a number of normal lymphocytes, but normal-looking monocytes were rarely seen. The distinct ultrastructure of LRE cells supports the validity of LRE as a clinicopathologic entity. (56 refs.)

- 77-0391 Terminal Deoxynucleotidyl Transferase in Normal and Neoplastic Hematopoietic Cells.** (Eng.) McCaffrey, R.; Harrison, T. A.; Kung, P. C.; Parkman, R.; Silverstone, A. E.; Baltimore, D. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): Haematol Bluttransfus vol. 19, pp. 503-513; 1976.

The activity of terminal deoxynucleotidyl transferase (Tdt) in neoplastic cells was assayed. Immediately before the tissues were homogenized, 20 mM phenylmethylsulfonyl fluoride and 5% ethanol were added to inhibit the proteolytic degradation of Tdt when samples containing cells rich in proteolytic activity were studied. After detergent treatment, the crude homogenate was extracted with high salt, resulting in a more efficient enzyme solubilization. Tdt activity was then identified following phosphocellulose chromatography of the crude homogenate. Tdt activity was identified in the leukemic cells of 32/36 patients clinically considered to have acute lymphoblastic leukemia (ALL). Children and adults representing both T-cell and null-cell disease were sampled. Tdt was not confined to the leukemic cells from patients considered to have ALL by the usual clinical and morphological criteria. Eight of 22 patients with blast crisis chronic myelogenous leukemia had Tdt-positive cells; however, only 3/8 enzyme-positive samples were felt to have lymphoblastic morphology

by their physicians. Some patients with undifferentiated leukemic cell morphology and monomyelocytic leukemia also had Tdt-positive cells. The Tdt activities noted in these non-ALL samples were similar, in terms of chromatographic pattern, to the ALL samples. The phosphocellulose elution pattern of Tdt from human thymocytes was similar to leukemia cell Tdt. When thymocytes were further separated on a discontinuous bovine serum albumin gradient and assayed for Tdt, the enzyme activity was maximally expressed. There existed in normal bone marrow a population of cells that expressed Tdt activity. In man, the phosphocellulose chromatographic pattern was a broad peak, eluting between peaks I and II. It was similar to the pattern observed when bone marrow cells from ALL patients with acute bone marrow relapse were analyzed. Tdt-positive normal cells should be fruitful populations for studies involving leukemogenic agents or events. (20 refs.)

- 77-0392 Leukemic Anaplasias Reflecting Physiologic Cytogenesis of Myeloid System.** (Eng.) Parwaresch, M. R.; Muller-Hermelink, H. K.; Lennert, K. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 95-98; 1976.

Cytochemical techniques that can be used as chemical markers for the identification of granulocytes of myeloproliferative disease are reviewed. The naphthol AS-D chloroacetate esterase reaction is normally used to visualize promyelocytic azurophil granules and the neutrophilic cell line; however, basophils and eosinophils positive to this reaction have been reported in cases of myeloproliferative diseases. Granulocytes which possess specific eosinophil as well as basophil granules have been found in bone marrow and peripheral blood of patients with myeloproliferative disease. These are positive to the chloroacetate esterase reaction, toluidinblue staining for the demonstration of metachromasia, and the paradimethylaminobenzaldehydnitrite (Adams) reaction. The existence of a common promyelocyte from which neutrophils, monocytes, basophils, and eosinophils originate is proposed. (15 refs.)

- 77-0393 Proliferative Behavior of Hemopoietic Cells in Preleukemia and Overt Leukemia Observed in One Patient.** (Eng.) Dormer, P. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gall, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 91-94; 1976.

Hemopoietic cell proliferation was studied during preleukemia and overt leukemia in a 71-yr-old woman who developed acute myelogenous leukemia 2 yr after suffering from preleukemia characterized by peripheral pancytopenia and hypercellular bone marrow with ineffective erythropoiesis.

The phase of pancytopenia (anemia of 7.9 g% of Hb, leukopenia of 1240/mm³, and thrombocytopenia of 24,000/mm³) was retrospectively classified as preleukemia. After unsuccessful therapy with vitamins B₆, B₁₂, and folic acid, the patient received only occasional transfusion of packed RBC. She remained under outpatient control and did not show significant changes over the next 20 mo. A gradual rise in the WBC count with an increasing number of myeloblasts in the blood smear was then observed. AML developed 2 yr after the first examination. The relative production rates (cells produced per unit of time per 100 proerythroblasts) for myeloblasts, promyelocytes, myelocytes, proerythroblasts, basophilic erythroblasts, and polychromatic erythroblasts in the bone marrow during the preleukemic period were: 11, 12, 12, 100, 130, and 70, respectively. The corresponding values during overt AML were: 640, 89, 106, 100, 141, and 88, respectively. A transition from steady state growth of myeloblasts to some kind of exponential expansion is postulated to explain how the myeloblasts in preleukemia (characterized by a reduced proliferative activity as well as a very low production rate) grew faster than the other cell types and attained such a high rate of new cell formation in AML. (3 refs.)

77-0394 An Electron Microscopic Study of the Spleen of the Rat in an Acute Myelogenous Leukemia.

(Eng.) Chen, L. T. (Dept. Anatomy, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Handler, E. E. *Anat Rec* 187(1): 29-46; 1977.

An ultrastructural investigation of the spleens of 18 rats with acute myelogenous leukemia is presented. Leukemic myeloblasts were readily distinguishable from other cells in the spleen. They contained numerous ribosomes and a few small granules. The nuclear membrane frequently had projections into the cytoplasm. In the early stage of leukemia, few leukemic myeloblasts were observed in the red pulp. In the late stage, the number of leukemic myeloblasts varied from one to the other. Leukemic myeloblasts appeared in groups in the cordal space of the red pulp and marginal zone and occasionally encroached upon, but did not appear to penetrate, the white pulp. Leukemic myeloblasts seemed to infiltrate the spleen via the routes through which the normal blood cells traversed, through the meshwork of the cordal space. Proliferation of the leukemic myeloblasts was noted in the cordal space. Active splenic erythropoiesis was observed in spleens of the late stage of leukemia. Most of the developing RBC were located in the cordal space of the red pulp and were noted in groups at different stages of development. Many developing RBC lay adjacent to the sinus wall. Macrophages in the cordal space phagocytosed the extruded nuclei of the developing RBC. Foci of normal granulopoiesis were also observed in the late stage of leukemia. Developing granulocytes and megakaryocytes were seen in the cordal space. Immature megakaryocytes were scattered in the cordal space, but maturing megakaryocytes were near or against the sinus, and their peripheral cytoplasm extended into the sinus through interendothelial slits. The degree of splenic hematopoiesis and splenomegaly corresponded to the number of leu-

kemic myeloblasts in the spleen. Type C virus particles were noted in the intercellular space between leukemic myeloblasts. The splenic sinus walls may play a role in promoting compensatory hematopoiesis in the spleen. (16 refs.)

77-0395 The Incidence and Characteristics of Acute Myeloid Leukemia Arising in Hodgkin's Disease.

(Eng.) Larsen, J. (Dept. Oncology Radiotherapy, Odense Univ. Hosp., 5000 Odense, Denmark) Brincker, H. *Scand J Haematol* 18(3): 197-206; 1977.

The occurrence of acute myeloid leukemia (AML) in patients with Hodgkin's disease (HD) was assessed using records of the Danish Cancer Registry. The expected incidence of AML in 201 consecutive HD patients was 0.04, but 3 cases were observed, corresponding to a 75 times greater incidence. Cases recorded as "myeloid" and "other and unspecified" were assumed to represent nonlymphocytic leukemia. If all types of leukemia were considered, the expected number of cases was 0.08, corresponding to a 37.5-fold increase of the risk of leukemia. In both calculations, the difference between the expected and the observed number of cases was significant ($p < 0.01$). The authors also analyzed 44 additional individually reported cases of AML arising in HD, in addition to the 3 cases mentioned. The mean interval from the diagnosis of HD to the diagnosis of AML was 5.7 yr (range 0-19 yr). A total of 45% of the cases was myelomonocytic or monocytic, 48% were myeloblastic or undifferentiated, and 7% were erythroblastic. Only one partial and two complete remissions were obtained in the 47 patients. There was no evidence that polychemotherapy was associated with a higher risk of leukemia than single-drug chemotherapy. AML arising in HD differs from spontaneous cases of AML by having a low male/female ratio (0.84), by having a poor response to antileukemic chemotherapy, and by appearing in a younger age group. (49 refs.)

77-0396 Trisomy 8 in Acute Myeloid Leukemia: A Non-random Event. Lack of Correlation with Prognosis and Cytokinetic Parameters.

(Eng.) Philip, P. (Dept. Medicine A, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark) Wantzin, G. L.; Jensen, M. K.; Drivsholm, A. *Scand J Haematol* 18(2): 163-169; 1977.

The chromosomes of 16 patients with acute myelogenous leukemia (AML), 15 of whom were previously untreated, were analyzed. In 6 patients, an extra chromosome 8 was the only abnormality in practically all analyzable mitoses; the remaining 10 patients had a normal chromosome complement in their bone marrow cells. The possible influence of trisomy 8 on several clinical and cytokinetic parameters was investigated. There were no significant differences between the two groups with respect to age, sex, survival, Hb content, WBC and platelet counts, percent myeloblasts and promyelocytes in blood and marrow, percent stabs and segmented cells in blood and marrow, and percent erythroblasts. Of the total

of 22 AML patients with chromosomal aberrations, seen by the authors, the supernumerary chromosome 8 was present in 36%, compatible with the hypothesis of a nonrandom event. (13 refs.)

- 77-0397 Pathogenesis of Central Nervous System Infiltration in Acute Leukemia.** (Eng.) Azzarelli, B. (Inst. Pathology, Case Western Reserve Univ., 2085 Adelbert Road, Cleveland, OH 44106) *Arch Pathol Lab Med* 101(4): 203-205; 1977.

The distribution pattern of leukemic infiltrates was examined in 31 autopsy cases with CNS involvement (17 acute myeloblastic leukemia, AML, and 14 cases of acute lymphocytic leukemia, ALL). Infiltrates were found in the dura mater of 29/31, in the arachnoid of 22/31, and in the brain parenchyma of 5/31. In nine cases, infiltration of the dura mater was the sole manifestation of the disease. Only three showed isolated involvement of the arachnoid without evidence of leukemic cells in the dura mater. Parenchymal involvement was only found in those areas that also showed a massive Virchow-Robin space infiltrate. The most common finding was perivascular infiltration in the dura mater, which consisted of a focal aggregate of leukemic cells surrounding the veins (22/31 cases). Perivascular leukemic deposits in the mater may result from hemorrhage, diapedesis, or as a direct extension from the adjacent skull marrow. The pattern of CNS involvement appears to follow an anatomic gradient, which starts in the bone marrow and ends in the brain tissue by way of the perivascular adventitial tissue connecting the dura mater and the subarachnoid space. (9 refs.)

- 77-0398 Chromosomal 6q-Anomaly in Acute Lymphoblastic Leukaemia [Letter to Editor].** (Eng.) Oshimura, M. (Roswell Park Memorial Inst., Buffalo, NY 14263) *Lancet* 2(8000): 1405-1406; 1976.

A possible non-random karyotypic change in acute lymphoblastic leukemia (ALL), consisting of a 6q-anomaly and affecting patients with this disease, is observed. Chromosomes were studied in the bone marrow cells from 101 patients with ALL since 1968. Aneuploidy was found in approx half of the cases, and the distribution of the chromosomal numbers was very similar to that of 106 cases studied before 1968, a large proportion of the patients having hyperdiploidy. The cells of 16 cases with chromosomal abnormalities were successfully examined with Q and G banded techniques. Four patients had a similar abnormality--partial deletion of the long arm of chromosome 6, two having a 6q- with additional abnormalities and two having 6q- as the sole karyotypic abnormality. The break point in chromosome 6 appeared to involve a segment from q21 to q25. Investigation of the surface antigens in the latter two cases revealed one to be typical T-cell ALL and the other of the null-cell variety. Chromosomal banding studies were performed on cell lines originating from thymus-derived lymphocytes (T cells) of the peripheral blood

from seven patients with ALL. Four of the seven cell lines had an abnormality similar to the one described (6q-). Three of the cell lines had other abnormalities in addition to the 6q-. The abnormality of chromosome 6 was not noted among 34 patients with acute myeloblastic leukemia (AML) studied with banding techniques. The frequency of the 6q- abnormality in ALL is at least as common as that of the non-random changes described for AML and presents another instance in which the finding of possible specific karyotypic abnormality in acute leukemia was made possible by the application of banding techniques. (4 refs.)

- 77-0399 Tetraploid Cell Line in a Girl with Acute Leukemia.** (Eng.) Foadi, M. D. (Dept. Haematology, Charing Cross Hosp.-Fulham, London W6 8RF, England) *Acta Haematol (Basel)* 57(1): 55-64; 1977.

The case report of a 9 1/2-yr-old girl with a 7 1/2-yr history of acute leukemia and with tetraploid malignant cells is presented. The girl was seen initially with polymyositis, extensive bruising over the legs, and splenomegaly. A diagnosis of acute stem leukemia was made from findings in the bone marrow, in which nearly all cells were large and immature, with scanty cytoplasm and clefted nuclei. After remission was induced, the patient remained well with no chemotherapy for 6 yr. She then was noted to have bleeding, purpura, and ecchymoses. There was hepatosplenomegaly and a large mass rising up to the umbilicus, which was thought to be ovarian in origin. Treatment with prednisone and 6-mercaptopurine was instituted. However, a final relapse was complicated by septicemia, and the patient died shortly thereafter. The malignant cell line in the bone marrow and peripheral blood was determined to be tetraploid. The tetraploid DNA content of the blast cells distinguished them from the other cells in the bone marrow and blood of this patient and from the blast cells found in other cases of acute lymphoblastic leukemia. (21 refs.)

- 77-0400 Chronic Lymphatic Leukaemia, Malignant Melanomas and Mosquito Hypersensitivity.** (Eng.) Liden, S. (Dept. Dermatology, Univ. Hosp., Univ. Umea, Umea, Sweden) Back, O.; Tarnvik, A. *Acta Derm Venereol (Stockh)* 57: 81-83; 1977.

Chronic lymphatic leukemia (CLL), malignant melanoma, and hypersensitivity to mosquitoes occurred simultaneously in a retired forestry officer. In 1972, CLL was diagnosed. This malignancy has remained quiescent, leaving the patient in good general health and not requiring therapy. In 1972, he also had an episode of herpes zoster. He first noted an exaggerated reaction to mosquito bites (*Culex pipiens*) that gradually worsened over the following years. In the summer of 1975, a black nodule was observed in the skin over the left scapula. Clinically, it was strongly suspected to be a malignant melanoma. This diagnosis was confirmed histologically. A wide excision was made. No axillary lymph nodes were

palpable. Early in 1976, a malignant melanoma behind the left ear was diagnosed and subsequently excised. There may be possible links between the unusual clinical picture in the patient and certain disturbances in his immune system. (10 refs.)

- 77-0401 Philadelphia Chromosome in Acute Lymphocytic Leukemia.** (Eng.) Philip, P. (Div. Haematology, Dept. Medicine A, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark) Muller-Berat, N.; Killmann, S. *Hereditas* 84(2): 231-232; 1976.

Philadelphia (Ph¹) chromosomes were found in bone marrow cells of a patient with acute lymphocyte leukemia (ALL) by banding methods. When the marrow contained nearly 100% blast cells, all mitoses had a Ph¹ chromosome. During a later relapse, 9/16 analyzed mitoses were normal; 7 carried a Ph¹ chromosome as a result of a translocation between chromosomes 9q;22q-. These chromosome data indicate that a link may exist between ALL and chronic myeloid leukemia. (9 refs.)

- 77-0402 Pyoderma Gangrenosum, Defective Neutrophil Chemotaxis, and Leukemia (Letter to Editor).** (Eng.) Shore, R. N. (Philadelphia, PA) *Arch Dermatol* 112(12): 1792-1793; 1976.

The development of acute myeloblastic leukemia is reported in a patient with polycythemia vera, pyoderma gangrenosum, and an intrinsic cellular defect in neutrophil chemotaxis. The leukemia occurred within a year of the onset of pyoderma gangrenosum and the demonstration of defective chemotaxis. Both the cutaneous lesions and the neutrophil abnormalities may have been early signs of the leukemic process. The association of pyoderma gangrenosum and leukemia has been described in at least eight other patients. (23 refs.)

- 77-0403 Ultrastructure of Chronic Lymphocytic Leukemia.** (Spa.) Martinez-Penuela Garcia, J. M. (Hosp. Civil Navarra, Laboratorio Clinico, Pamplona, Spain) Orue Lecue, M. T.; Gastearna Erice, J. *Sangre* 21(4): 794-804; 1976.

Twelve cases of chronic lymphatic leukemia were clinically and hematologically studied. The ultrastructure of the lymphatic cells in bone marrow and the lymph nodes is described. The coexistence of two different cell clones was found only once. Several aspects of the nucleus and protoplasm are described. The cell line in the lymph nodes showed wavy connections with no reinforcement of the membrane or desmosomes. Pseudopods and pinocytic openings were frequent in isolated cells of bone marrow. (12 refs.)

- 77-0404 Freeze-Fracture of the Normal and Pathological Megakaryocyte Lineage in Chronic Megakaryocytic-Granulocytic Myelosis.** (Eng.) Thiele, J. (Pathologisches Institut Medizinischen Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany) Ballard, A. C.; Georgii, A. *Virchows Arch* 22(1): 33-51; 1977.

The demarcation membrane system (DMS) of pathological megakaryocytes was investigated by comparison of thin sections with freeze-fracture replicas of the human bone marrow of chronic megakaryocytic-granulocytic myelosis (CMGM). The DMS of CMGM showed no connections with the Golgi apparatus or rough-surfaced endoplasmic reticulum, but originated from tubular infoldings of the plasma membrane. These infoldings were always in continuity with the extracellular space and formed an intracellular membranous pool by the branching and coalescing of flattened tubules from which the perforated cisternae of the DMS arise. The freeze-fracture of normal thrombocytes confirmed earlier findings. The abnormal giant platelets seen in CMGM displayed extensive areas of smooth membranes of a spongy structure consisting of dense tubules surrounded by the labyrinth of the surface-connected system. The physiological significance of the tubular areas of these atypical platelets remains unsolved. (35 refs.)

- 77-0405 Myeloperoxidase and Lactoferrin of Blood Neutrophils and Plasma in Chronic Granulocytic Leukaemia.** (Eng.) Olofsson, T. (Dept. Internal Medicine, Res. Dept. 2, E-blocket, Univ. Lund, S-22185 Lund, Sweden) Olsson, I.; Venge, P. *Scand J Haematol* 18(2): 113-120; 1977.

Myeloperoxidase (MPO), which is restricted to primary granules, and lactoferrin, which is restricted to secondary granules, were determined in the blood plasma and neutrophils of 17 patients with chronic phase chronic granulocytic leukemia (CGL). Plasma lactoferrin levels were found to be increased two to eight times, MPO levels two to three times. A correlation was found between cellular and plasma levels for lactoferrin, but not for MPO, which indicates that plasma lactoferrin is released from circulating WBC, whereas MPO is not. Both compounds showed a correlation with WBC counts. Neutrophil lactoferrin was decreased in 71% of the CGL patients, but MPO was decreased in only 18%. Serial studies on individual patients indicated low cellular lactoferrin levels during phases with rapidly expanding leukocytosis, which suggests a defective maturation of neutrophils or an abnormal release due to a prolonged intravascular life span. (24 refs.)

- 77-0406 Megakaryoblastic Transformation of Chronic Granulocytic Leukaemia. An Electron Microscopy and Cytochemical Study.** (Eng.) Bain, B. (MRC Leukaemia Unit, Royal Postgraduate Medical Sch., DuCane Road, Shepherd's Bush, London W12 0HS, England) Catovsky,

D.; O'Brien, M.; Spiers, A. S.; Richards, H. G. *J Clin Pathol* 30(3): 235-242; 1977.

Morphological, cytochemical, and ultrastructural electron microscopic studies were performed on the blood and bone marrow cells of a 44-yr-old woman with Philadelphia chromosome (Ph⁺)-positive chronic granulocytic leukemia in megakaryocytic acute transformation. The entire leukemic cell population consisted of megakaryoblasts and megakaryocytes. All stages of maturation were present between the blasts and the mature micromegakaryocytes. The continuous spectrum of cells, the myeloperoxidase negativity of the granules, and the presence of some blasts showing the early stages of formation of demarcation membranes suggested that the relatively undifferentiated blasts were megakaryoblasts rather than myeloblasts or monoblasts. In addition to the myeloperoxidase negativity, both blasts and micromegakaryocytes were negative for Sudan Black B and the cytochemical tests for lysozyme. The pattern of positivity with the PAS, naphthol AS acetate esterase, and acid phosphatase reactions was almost identical with that observed in normal megakaryocytes. The sheep RBC rosette test gave a negative result, and no surface immunoglobulins were detected. There was no reaction with an anti-acute lymphoblastic leukemia serum or with an anti-granulocyte serum, but there was a weakly positive one with an anti-acute myeloid leukemia serum. The occurrence of megakaryoblastic and erythroblastic transformation supports the evidence derived from cytogenetic and biochemical studies showing that the disease involves a pluripotential stem cell. (25 refs.)

77-0407 Myelomonocytic Leukaemia with a Preleukemic Syndrome and Ph⁺ Chromosome in Monozygotic Twins. (Eng.) Svarch, E. (Instituto de Hematologia e Immunologia, Apartado 8070 Havana, 8, Cuba) De La Torre, E. *Arch Dis Child* 52(1): 72-74; 1977.

The occurrence of myelomonocytic leukemia associated with the Ph⁺ chromosome in monozygotic twins is reported. The first twin was admitted to the hospital for the first time in May 1970 at age 7 with frequent and severe epistaxis. Up to January 1973, he suffered almost daily from epistaxis, sometimes associated with petechiae and ecchymoses. Laboratory and x-ray studies were repeatedly normal. In 1973, he presented with a generalized *Alkaligenes faecalis* infection, severe bilateral bronchopneumonia, and a bleeding gum hypertrophy. He was now found to have a pancytopenia, with 16% monocytoid blast cells. He was discharged with a diagnosis of preleukemic syndrome. In November 1973, he died with generalized sepsis due to *A. faecalis*. The main features at necropsy were blast cell infiltration of the bone marrow, lymph nodes, spleen, and liver. The course of disease of the second twin was practically the same up to November 1972, when his platelets fell to low levels. In March 1973, monocytoid blasts appeared in peripheral blood. From this time onward, a progressive leukocytosis appeared up to 50,000/mm³, with blast cells up to 56%. He died in December 1973 with a generalized sepsis due to an unidentified microorganism.

Postmortem marrow aspiration showed massive monoblastosis. The karyotype studied during the final period of the disease in this twin demonstrated a Ph⁺ chromosome. The similarity of the clinical picture suggests the important role of genetic factors. (7 refs.)

77-0408 A New Chromosome Aberration in Chronic Myelogenous Leukemia. (Fre.) Berger, R. (Centre de Recherches de Biologie du Developpement Foetal, Hopital Port-Royal, 123, boulevard de Port-Royal, F75014 Paris, France) Gyger, M.; Bussel, A. *Nouv Rev Fr Hemato* 16(3): 309-319; 1976.

The case history of a 57-yr-old man with chronic myelogenous leukemia with myelofibrosis and failure to respond to busulfan therapy is presented. An abnormal clone with a rearrangement of four chromosomes, 46, XX, t(1;9)(q21;q24), t(6;22)(q26;q11) was observed. The possible significance of these chromosome abnormalities, which are different from the t(9;22) translocation of chronic myelogenous leukemia, is discussed. (27 refs.)

77-0409 Chronic Myelocytic Leukemia: Cytogenetic Findings and Their Relations to Pathogenesis and Clinic. (Eng.) Hossfeld, D. K. (Medical Univ. Clinic Tumor Res., Univ. Essen, 43 Essen 1, Hufelandstrasse, 55 W. Germany) *Ser Haematol* 8(4): 53-74; 1975.

The chromosome constitution of the myeloid cells of 106 patients with chronic myeloid leukemia was analyzed and its relation to age, sex, and survival investigated. Seventy patients were in the chronic and 36 in the blastic phase. At the time of the first chromosome analysis the majority of the patients (59.8%) had already been treated, mainly with busulfan. Whenever possible, bone marrow cells were used to establish the karyotype—at least 25 metaphases of each specimen were analyzed. The Ph⁺ chromosome was demonstrated in 85.9% of the patients. A mixture of Ph⁺-positive and Ph⁺-negative metaphases was found in 10 patients in the chronic phase, half of whom were untreated. The chromosome bands of 22 cases were analyzed, and the results corroborated the impression of a nonrandom involvement of certain chromosome groups given by statistical analysis. Chromosomal findings in medullary and extramedullary tissues suggest an accumulation of cells with additional anomalies in extramedullary sites. Ph⁺-negative patients were older and had a survival shorter than Ph⁺-positive patients. The median survival time of patients in the blastic phase may be longer in those without additional chromosome anomalies. Hemoglobin concentration, the number of platelets, and the percentage of myeloblasts in the bone marrow also had a definite influence on survival times. The study confirmed the unique prognostic implication of the chromosomal status, but indicated that for the individual patient a more accurate prognostic statement can be made by combining the hematological and chromosomal findings. (26 refs.)

77-0410 Comparative Cytogenetic Studies of Bone Marrow and Extramedullary Tissues in Chronic Myeloid Leukemia. (Eng.) Mitelman, F. (Dept. Clinical Genetics, Univ. Hosp., S-221 85 Lund, Sweden) *Ser Haematol* 8(4): 113-117; 1975.

A direct technique for the study of chromosomes has been developed and used to study bone marrow cells and spleen cells in 12 patients with chronic myeloid leukemia (CML). On the initial examination in the untreated chronic stage, all patients had 85%-100% Philadelphia chromosome (Ph¹)-positive diploid cells in both sites, with no other karyotypic abnormalities. In six patients, still in the chronic stage, this has remained unchanged on subsequent examinations 5-16 mo after the first examination. In two patients, cell clones with additional karyotypic changes have appeared during the course of the disease. In these patients the abnormal cell clones were found in the spleen before they were observed in the bone marrow, and the appearance of these chromosome aberrations in the spleen preceded clinical and morphologic signs of blastic transformation in the bone marrow and the peripheral blood. The results indicate that in CML, the spleen may play a significant role not only as a reservoir of Ph¹-positive cells but also in the transformation of the chronic phase into the final blastic stage. In three recent publications, a much higher frequency of Ph¹-positive cells with additional karyotypic changes were reported in the spleen than in the bone marrow. Megaloblastoid changes are more common in the spleen than in the bone marrow, and the proportion of basophilic WBC is significantly larger in the spleen. The demonstration of an increase of T lymphocytes in the spleen in CML in contrast to nonmalignant spleens, where there is a predominance of B lymphocytes and a paucity of T lymphocytes, further implicates the spleen in the pathogenesis of CML. (17 refs.)

77-0411 Monomyelocytic Leukemia in an Untreated Case of Waldenstrom Macroglobulinemia. (Eng.) Salberg, D. (Dept. Immunology, Univ. Michigan Sch. Medicine, Ann Arbor, MI) Kurtides, E. S.; McKeever, W. P. *Arch Intern Med* 137(4): 514-516; 1977.

Monomyelocytic leukemia developed, unaided by any antineoplastic therapy, in the presence of Waldenstrom macroglobulinemia in a 68-yr-old woman. The patient was seen in May 1970 with pneumonia. A bone marrow examination revealed increased numbers of plasmacytoid cells. A diagnosis of Waldenstrom macroglobulinemia was made, but treatment was not elected. The patient remained asymptomatic until February 1974, when she was readmitted for pneumonia. On this occasion, hepatomegaly and splenomegaly were discovered. The bone marrow showed hypercellularity, with increased granulocytes at all phases of maturation and an abundance of myeloblasts and promyelocytes. The serum and urine lysozyme levels were consistent with a diagnosis of monomyelocytic leukemia. Combination chemotherapy consisting of vincristine sulfate, cytarabine, thioguanine, and prednisone led to a partial remission to February 1976, when

she died after a 48-hr illness in full relapse with septicemic shock, disseminated intravascular coagulation, and acute renal failure. (23 refs.)

77-0412 Banded Karyotypes of H-4-IIE-C3 Rat Hepatoma Cells Grown in Vitro. (Eng.) Mullen, V. T. (Dept. Biology, San Diego State Univ., San Diego, CA 92182) *In Vitro* 12(9): 658-664; 1976.

Banded karyotypes of H-4-IIE-C3 rat hepatoma cells grown in vitro were analyzed. Mitotic cells from the H-4-IIE-C3 line showed a range of 45-53 chromosomes/cell, with 75% displaying a chromosome number between 49 and 52. Detailed analysis of the H-4-IIE-C3 karyotypes was restricted to 22 Wright's-Giemsa stained cells, which exhibited 49-53 chromosomes. Twenty-one structurally abnormal chromosomes were identified in these cells, and the origin of 9 could be determined. Only one (M-1) occurred with enough frequency to be of use as a marker. It appears to be a Robertsonian translocation involving chromosomes 2 and 10. The findings indicate that the cell-to-cell difference in chromosome number is due to a random gain and loss of chromosomes and not to a gain or loss of a specific chromosome or set of chromosomes. (23 refs.)

77-0413 Chromosome Findings in Monoclonal Gammopathies. (Ger.) Hellriegel, K. P. (Medizinische Universitätsklinik, Cologne, W. Germany) *Haematol Bluttransfus* 18: 369-375; 1976.

Results of chromosome analyses in six patients with Waldenstrom's disease (WD) and in two with cold agglutininemia (CA) are presented, and cytogenetic studies in monoclonal gammopathies are reviewed. Supernumerary C and G chromosomes were found in 3/100 mitoses in one case. Unusually long, acentric fragments were found in two diploid mitoses. In another case, a mitosis with 47 chromosomes and a large submetacentric marker chromosome and three mitoses with 48 chromosomes and large, supernumerary submetacentric and medium-sized metacentric chromosomes were found; another two mitoses were pseudodiploid. Apart from incidental unspecific structural anomalies, no chromosomal aberrations were found in the other four cases of WD nor in the two patients with CA. The findings and related literature indicate that in WD, neoplastic cells are characterized by a hypo- to hyperdiploid karyotype with a large, usually metacentric or submetacentric marker chromosome. The marker chromosome is present in about 2/3 of all cases reported; it occurs usually in < 10% of all mitoses. Hypodiploid to hypotetraploid karyotypes are found in about 2/3 of all cases of multiple myeloma. Marker chromosomes are present in about 30% of all cases; they are usually acrocentric (14q+). The metacentric or submetacentric marker chromosomes cannot be considered specific for WD, because they are also encountered in multiple myeloma, acute leu-

kemia, and malignant lymphomas. There appears to be no correlation between the protein anomaly in the serum or urine and specific chromosomal aberrations. (32 refs.)

- 77-0414 G-banding in Rous Rat Sarcomas During Serial Transfer: Significant Chromosome Aberrations and Incidence of Stromal Mitoses.** (Eng.) Levan, G. (Inst. Genetics, Univ. Lund, Lund, Sweden) Mitelman, F. *Hereditas* 84: 1-13; 1976.

Four sc rat sarcomas, originally induced by Rous sarcoma virus (RSV), were chromosomally studied; they were then serially transplanted sc to Wistar/Furth rats and studied by means of a trypsin-versene G-band method. The metaphase RSV rat sarcomas had either well-spread, elongated chromosomes with distinct features, some with an abnormal chromosome set, or less well-spread, short, "fuzzy" chromosomes, usually with a normal karyotype. The karyotypes of the primary tumors were 43,XX,+B; 45,XY,+2B,+C13; 44,XY,+B,+C13; normal; 44,XY,+2B; 43,XY,+B. The karyotypes of the serially transplanted tumors were normal; 43,XX,+B; 44,XY,+B7,+C13; 43,XX,-A3,+C13,+mar2; 43XX,-A3,+C13,-D18,+mar2,+mar3; 44,XY,+B7,B9. The sex chromosomes in some cells of the transplanted tumors were not concordant with those of the animal in which the tumor had been originally induced; this applied only to cells with normal karyotype or those with a loss of one or two chromosomes. The results indicate that in the development of RSV-induced tumors in rats the virus interacts with the genetic material of an original host cell, transforming it into a malignant state; this initial step may involve chromosome aberrations. The substance that stimulates division of the normal cells is probably secreted by the transformed cells. (30 refs.)

- 77-0415 Multiple Myeloma. Orbital Involvement in a Youth.** (Eng.) Levin, S. R. (Dept. Ophthalmology, Univ. Cincinnati Coll. Medicine, Cincinnati, OH) Spaulding, A. G.; Wirman, J. A. *Arch Ophthalmol* 95(4): 642-644; 1977.

Orbital involvement by multiple myeloma, which rarely occurs in young individuals, is reported in a 19-yr-old pregnant black woman. The patient had a 2-wk history of bulging of the left upper lid and a 1-wk history of double vision. Roentgenograms of the skull and tomograms of the orbit revealed a destructive lesion extending into the roof of the orbit and involving the frontal bone. A chest roentgenogram demonstrated a destructive lesion in the outer third of the right clavicle and a suspicious area in the left distal clavicle. A computerized axial tomogram showed a smoothly outlined, sharply circumscribed lesion emanating from the cranial vault. Treatment consisted of actinomycin D (500 mg/day for 6 days) and irradiation to the orbit (2,700 rads). Following irradiation, there was a full return of extraocular muscle function and a gradual subsidence of the proptosis. The ul-

trastructure of the cells was characteristic of the malignant plasma cells of multiple myeloma. Multiple myeloma must now be included in the differential diagnosis of orbital lesion in young patients. (17 refs.)

- 77-0416 An Animal Model for Human Osteosarcoma** (Eng.) Singh, I. (Orthopaedic Res. Labs., Dept Surgery, Medical Coll. Ohio, Toledo, OH) Hatheway, J. M. Tsang, K. Y.; Blakemore, W. S.; McAllister, R. M. *Surgery* 81(2): 168-175; 1977.

Cultivated TE-85 human osteosarcoma cells were infected with murine sarcoma virus (MSV) (RD-114) and injected into antilymphocyte serum (ALS)-treated newborn hamsters in an attempt to develop a model for human osteosarcoma. A suspension of 1×10^6 cells injected sc produced encapsulated, undifferentiated sarcomas that could be transplanted successfully into other ALS-treated hamsters. When 2×10^6 cells were injected adjacent to the femur or the scapula, nonencapsulated osteosarcomas were formed. Tumors were palpable 10 to 14 days after injection and grew progressively until the death of the animal; mean survival time was 30 days. All animals had pulmonary metastases at autopsy. Electron microscopy of osteosarcomas adjacent to bone revealed the presence of collagen and nonmineralized osteosis; these tumors resembled human osteosarcomas in their morphology and biological behavior. In contrast, neither the pulmonary metastases nor the sc sarcomas contained bone or osteoid. Cultured TE-85-M-MSV cells and hamster tumors formed by these cells exhibited type C virus particles in the cytoplasmic vacuoles. Chromosome analysis of hamster tumor cells on the third passage in tissue culture showed the same chromosome composition and marker chromosome as the cultured TE-85 cells. (17 refs.)

- 77-0417 Bone Infarction Complicated by Sarcomatous Change. A Case Report.** (Eng.) Heselson, N. G. (Dept. Radiology, Univ. Cape Town, Cape Town, South Africa) Webber, B. L.; Goldberg, S.; Mills, E. E. *S Afr Med J* 50(48): 1942-1944; 1976.

A case history is presented of a patient with a sarcoma of the tibia associated with multiple bone infarcts. The patient was a 51-yr-old sailor in whom radiological examination of the upper right tibia demonstrated the presence of a large lytic lesion with irregular, poorly defined margins in the metaphysis and an overlying fine linear periosteal reaction. Within this area of destruction there was a well-demarcated area of calcification that resembled a bone infarct. Bilateral bone infarcts were demonstrated in the lower and upper tibial metaphyses and distal femoral metaphyses. An above-knee amputation of the right leg was performed, and chemotherapy comprising vincristine, methotrexate, and leucovorin rescue given every 3 wk for 6 mo was initiated. The patient was free of disease 15 mo after amputation. A review of the literature indicated that the association of bone infarction and sarcoma

is extremely rare, only 10 cases having been reported since the original description of such a case in 1960. All but one of the patients were men, and the average age was 56 yr. Multiple bone infarcts were seen in 9/10 cases. The follow-up of patients has been too short for definite conclusions, but five have died of metastases, four within 1 yr of the diagnosis. Two patients are alive and well after 1 yr and 5 yr, 7 mo, respectively. Of the 10 cases, 3 were malignant fibrous histiocytomas, 3 fibrosarcomas, and 3 osteosarcomas. The present case is the fourth instance of a fibrosarcoma. It is concluded that the association of bone infarcts and sarcoma may be fortuitous and that the rarity of the association does not warrant routine follow-up radiological examination. (8 refs.)

77-0418 Familial Occurrence of Histiocytosis. (Eng.) Frisell, E. (Dept. Pediatrics, Univ. Hosp. Umea, S-901 85 Umea, Sweden) Bjorksten, B.; Holmgren, G.; Angstrom, T. *Clin Genet* 11(3): 163-170; 1977.

The clinical and autopsy findings of four siblings in two sibships who died from histiocytosis are described. The children ranged in age from 2 wk to 2 mo on admission to the hospital. Hepatosplenomegaly and enlarged lymph nodes were seen in all four children. Most organs showed a massive, mainly perivascular, cellular infiltration of lymphocytes and histiocytes of varying degrees of maturity, including macrophages showing erythrophagocytosis. Sections of liver, spleen, lymph nodes, and bone marrow were stained with fat stain and PAS stain with negative results. In three cases the bone marrow showed varying degrees of aplasia, but in the fourth case it was hyperplastic. Consanguinity between the parents was established for one of the sibships, which belonged to a pedigree in which malignant disease occurred in two generations. The observations indicate that the type of histiocytosis is caused by homozygosity for a single recessive gene. The development of malignancy in the father and paternal grandfather of two of the cases suggests either (1) that the heterozygotic state may be associated with malignancy, but the homozygous condition may lead to histiocytosis, or (2) that a single gene with variable penetrance is instrumental. (18 refs.)

77-0419 Breast Cancer in Identical Twins. (Eng.) Normann, E. (Surgical Dept. III, Ulleval Hosp., Oslo, Norway) *Acta Chir Scand* 142(7): 541-542; 1976.

The case histories of 59-yr-old twin women, each with a breast cancer in the left breast, are presented. Both were nulliparous. One had her appendix removed at the age of 25 and the other at 27 yr; both received surgery for acute conditions. These women were admitted and treated for breast cancer within 3 yr of each other. One underwent simple mastectomy and the other, radical mastectomy; no metastases were found. Although the coincidence of breast cancer in twins is rare, such patients, as well as other first degree relatives, should be seen biannually to annually for examination of the contralateral breast. (12 refs.)

77-0420 The Possible Relationship Between Mammary Dysplasia and Breast Cancer. (Eng.) Renwick, S. B. (149 Macquarie St., Sydney, New South Wales, Australia) *Aust NZ J Surg* 46(4): 341-343; 1976.

Available literature concerning a possible association between benign mammary dysplasia and carcinoma is reviewed. Four methods used to study this association include: (1) histological and temporal progression, (2) retrospective studies, (3) concurrent series, and (4) prospective studies. Some results obtained using these methods are tabulated. Prospective studies which follow up patients for a 5- to 10-yr period confirm an increase in the incidence of breast cancer in patients with clinical benign mammary dysplasia (10 times in one series) and in patients with biopsy-proved benign mammary dysplasia (5 to 11 times in various series). Close follow-up of such patients in breast clinics is recommended. (26 refs.)

77-0421 Glomus Structures in Axillary Lymph Nodes and Their Demarcation Against Metastases of Mammary Carcinoma. (Ger.) Huhn, F. O. (Frauenklinik im Dominikus-Krankenhaus Dusseldorf-Heerd, Am Heerdter Krankenhaus 2, D-4000 Dusseldorf 11, W. Germany) *Arch Gynaekol* 222(1): 95-102; 1977.

Microscopic investigations of axillary lymph node specimens excised from 400 patients with breast carcinoma were made. Metastases were found in 264 cases; they included 58 micrometastases, 74 macrometastases in one to two lymph nodes, and 132 large focal metastases in three or more lymph nodes. In addition, epithelioid cell clusters, identified as epithelioid glomus structures, were found in 18 cases. They were localized directly to the local vascular stroma. These clusters were only found in patients that were free from metastasis. (22 refs.)

77-0422 Lupus-like Syndrome Associated with Carcinoma of the Breast. (Eng.) Wallach, H. W. (8720 N. Kendall Drive, Miami, FL 33176) *Arch Intern Med* 137(4): 532-535; 1977.

A lupuslike syndrome associated with breast carcinoma occurred in two patients. A 56-yr-old woman was found to have a large, nonresectable adenocarcinoma of the left breast in October 1973. From January through February 1974, she received 5,000 rads to her chest wall with a 2,000-rad boost to the breast mass. In December 1974, the patient was seen with a 3-mo history of left-sided pleuritic chest pain and dyspnea on walking less than one-half block. The fluorescent antinuclear antibody (FANA) reaction was positive, with a titer of 1:100 and a speckled pattern, and a lupus erythematosus (LE) preparation was positive. A 62-yr-old woman was initially seen in October 1974 with masses in her left breast and left axilla of 1 yr duration. Biopsy of the left axillary node revealed metastatic adenocarcinoma consistent with a primary breast adenocarcinoma. She received 3,900 rads to the breast and 3,000 rads to the left supraclavicular and axillary

areas. In October 1975, the patient was admitted complaining of pleuritic chest pain and shortness of breath of 24 hr duration. The FANA reaction was positive, with a titer of 1:100 and a speckled pattern, and an LE preparation was positive. Radiation may have initiated an immunological response, leading to a lupuslike syndrome. (26 refs.)

- 77-0423 Immunoglobulin Concentrations in Cervical Mucus in Patients with Normal and Abnormal Cervical Cytology.** (Eng.) Coughlan, B. M. (Natl. Maternity Hosp., Dublin 2, Ireland) *Br J Obstet Gynecol* 84(21): 129-134; 1977.

The cervical mucus of 16 patients with an abnormal cervical cytology and 31 patients with a normal cytology was studied at each stage of the menstrual cycle for immunoglobulin M (IgM), IgG, and IgA. The mean Ig concentrations were determined for three arbitrarily chosen stages in the menstrual cycle: 6th to 13th days, 14th to 20th days, and 21st to 28th days. There was a significant increase in IgA concentration during the last week of the menstrual cycle in both groups of patients but with IgG this increase only reached significant levels in patients with an abnormal cervical cytology. These findings were reflected in the lower IgG/IgA ratio in the last week of the cycle. Patients with an abnormal cervical cytology had significantly higher IgA concentrations than patients with a normal cervical cytology. For IgG, the difference between patients with a normal and abnormal cytology was less striking. There was a significant correlation at each stage of the menstrual cycle between IgG and IgA for patients with a normal cervical cytology, but there was no correlation at any stage of the menstrual cycle in patients with an abnormal cervical cytology. Patients with an abnormal cervical cytology demonstrate increased IgG and IgA concentrations in their cervical mucus. (25 refs.)

- 77-0424 Ovarian Teratomas and Genetics of Germ-Cell Formation (Letter to Editor).** (Eng.) Hecht, F. (Dept. Pediatrics, Div. Perinatal Medicine, Univ. Oregon Health Sciences Center, Portland, OR 97201) McCaw, B. K.; Patil, S. *Lancet* 2(7998): 1311; 1976.

Ovarian teratomas appear to originate as parthenogens by self-fertilization. In meiosis, the second polar body is normally extruded and lost. Sometimes, however, the second polar body is not extruded or it re-fuses with the ovum. The self-fertilized ovum then goes on to form an ovarian teratoma. Ovarian teratomas are most frequently detected in the first two decades of life. Almost half of all ovarian tumors before age 20 are teratomas. Early onset is a common characteristic of hereditary tumors along with bilaterality, which occurs in 10%-25% of the patients. In one familial occurrence, a 25-year-old woman (from whom an ovarian teratoma had been resected at age 21) learned that her maternal grandmother, now 82, had also had an ovarian tumor that contained hair and teeth. In an animal model for genetically determined ovarian

teratomas (mice of the inbred LT strain), approx half the females develop ovarian teratomas. It is suggested that there are human genes that dictate the formation and fate of the second polar body; mutant genes may disturb this normal process and predispose a woman to form an ovarian teratoma. (11 refs.)

- 77-0425 Nosological Study of True Hermaphroditism and Mixed and Asymmetrical Gonadal Dysgenesis.** (Fre.) Fournier, J. L. (Hopital Regional, 59033 Lille, France) Saint-Aubert, P.; Ponte, C.; Gaudier, B.; Walbaum, R.; Farriaux, J. P.; Fontaine, G. *Ann Pediatr* 23(12): 763-775; 1976.

Twelve cases of true hermaphroditism and mixed and asymmetric gonadal dysgenesis were studied. The classical histological concept of hermaphroditism was enlarged: this concept, apart from true hermaphroditism, should include mixed symmetrical gonadal dysgenesis and/or asymmetric dysgenesis and type II testicular hypogenesis. All these diseases have similar embryopathogenic mechanisms; it is unimportant whether the ovary contains follicles, as required by the classical definition of true hermaphroditism. There was a high carcinogenic risk in the presence of gonosome. The following classification should be used: type I (46 XX) noncarcinogenic bigonadism and type II bigonadism, regrouping other chromosome formulas, with a high carcinogenic risk (the existence of a Y chromosome should be suspected even if not karyologically evident). Castration should be performed in all cases. (68 refs.)

- 77-0426 Primary Uterine Tumors and Multiple Endocrine Adenomatosis, Type I.** (Eng.) Dehner, L. P. (Box 76, Mayo Memorial Building, Univ. Minnesota, Minneapolis, MN 55455) Prem, K. A.; Delaney, J. P.; Weber, W. R.; Najarian, J. *Obstet Gynecol [Suppl]* 49(1): 41s-45s; 1977.

The clinical and pathologic features of multiple endocrine adenomatosis (MEA), Type I, initially diagnosed in a 35-year-old woman with primary chief cell hyperplasia of the parathyroids, are reported. A well-differentiated endometrial adenocarcinoma was recognized when vaginal bleeding developed 5 yr after parathyroidectomy. During hysterectomy, an adenomatoid tumor of the uterus and a nonbeta islet cell tumor of the pancreas were also found. The role of an observed enlarging sella turcica probably secondary to a pituitary adenoma is speculated upon. A possible relationship between the MEA syndrome and gynecologic neoplasms is discussed. (15 refs.)

- 77-0427 Oral Contraceptives and Endometrial Carcinoma: Case for Progesterone-Receptor Defect (Letter to Editor).** (Eng.) Jansen, R. P. (King George V Memorial Hosp., Sydney, New South Wales, Australia) Elliott, P. M. *Lancet* 1(8011): 602-603; 1977.

A 33-yr-old woman who had been taking the oral contraceptive Norlestrin (norethisterone plus ethinylestradiol) continuously for the preceding 7 yr presented with a 3-mo history of menorrhagia and intermenstrual bleeding. Histological examination of the tissue obtained by curettage showed a highly differentiated adenocarcinoma, with some isolated areas normal except for oral-contraceptive effects. Extrafascial hysterectomy and bilateral Salpingo-oophorectomy were performed. Postoperatively, radium was administered intravaginally. The patient is well at 4-yr follow-up. A discussion follows on the significance of the presence or absence of progesterone receptors in the development of endometrial carcinoma. The importance of investigating intermenstrual bleeding regardless of age, menstrual regularity, or mode of contraception is stressed. (16 refs.)

77-0428 The Ultrastructure of a Poorly Differentiated Adenocarcinoma of the Human Tuba Uterina. (Eng.) Rorat, E. (Queens Hosp. Center, 82-68 164th St., Jamaica, NY 11432) *Oncology* 33(4): 167-169; 1976.

The case history of a 49-yr-old woman with a poorly differentiated adenocarcinoma of the oviduct is presented. The tumor was studied by both light and electron microscopy. On one side, it was a well differentiated intraepithelial process and on the other a poorly differentiated adenocarcinoma. The cells of the adenocarcinoma contained abundant mitochondria, bound and free ribosomes, prominent Golgi bodies, and aggregates of membrane-bound dense bodies. That the neoplasm was ultrastructurally similar to poorly differentiated ovarian serous carcinomas supports the hypothesis that both tumors are derived from similar stem cells. (3 refs.)

77-0429 Simultaneous In Situ Carcinoma of the Cervix, Vulva and Perineum After Immunosuppressive Therapy for Renal Transplantation. (Eng.) Leckie, G. B. (Dept. Obstetrics Gynaecology, Nottingham Hosp. Women, Nottingham, England) *Br J Obstet Gynaecol* 84(2): 143-148; 1977.

The case of a 31-yr-old woman who developed synchronous in situ carcinomas of the cervix uteri, vulva, and perineal skin is reported. The patient was referred to the hospital in January 1975 with a 3-wk history of vaginal discharge associated with numerous painless "warts" of the vulva and perineum. The development of chronic renal failure due to chronic pyelonephritis had led to a successful cadaver donor renal transplantation in 1969. Subsequent to this, the patient had been treated continuously with azathioprine (125 mg) and prednisolone (12.5 mg) daily. In February 1975, the patient had a cone biopsy of the cervix and a biopsy of one of the larger vulval lesions. Histological examination of the cervical tissue demonstrated extensive and severe dysplastic abnormalities of the epithelium with foci of in situ carcinoma that extended into the mucous gland ducts in the endocervix, but with no evidence of invasion. The vulval biopsy showed florid

intraepidermal carcinoma, also without evidence of invasion. Local vulvectomy was performed, and the perianal skin was removed. In September 1976, there was no vulval or perianal abnormality, and the cervical smear was normal. There is concluded to be a risk of epithelial and lymphomatous malignancies in renal transplant recipients due to the long-term immunosuppressive therapy. (6 refs.)

77-0430 Adenosquamous Carcinoma of the Endometrium. (Eng.) Haqqani, M. T. (Dept. Pathology, Univ. Manchester, Manchester, England) Fox, H. *J Clin Pathol* 29(11): 959-966; 1976.

Of 675 malignant endometrial tumors seen in a Manchester, England hospital from 1956 to 1975, 34 were considered adenosquamous, for an overall incidence of 5%. There was no notable increase during this period. The diagnostic criterion of adenosquamous carcinoma was the presence of both malignant squamous and malignant glandular tissue within the same neoplasm. The glandular components of these tumors demonstrated all the well-recognized characteristics of adenocarcinoma. Most adenosquamous carcinomas contained well-differentiated Grade G1 glandular tissue; only a minority were of Grade G2, and none were G3. In all the cases, the adenocarcinomatous element was the predominant feature of the tumor, and in none did it account for less than 70% of the neoplastic tissue. The malignant squamous epithelium sometimes occurred in close proximity to, or even in apposition with, the malignant glandular tissue, but more often the two components were separated by connective tissue. There was no true intermingling of squamous and glandular tissues, and malignant squamous epithelium was not noted within a glandular lumen. The squamous carcinomatous tissue was not in continuity with glandular epithelium, and transitional forms were not seen. The malignant squamous epithelium was rarely of the frankly keratinizing variety, although individual cell keratinization was observed. The cells were large, with a variable degree of pleomorphism and mitotic activity, they were polygonal or elongated with indistinct cell boundaries and very few intercellular bridges, and they had an abundant, homogeneously acidophilic cytoplasm and centrally placed nuclei with irregularly distributed chromatin. In almost one-third of the adenosquamous carcinomas, benign metaplastic squamous epithelium was also present. There was a poorer survival rate for patients with adenosquamous carcinoma than for those with endometrial adenocarcinoma. The currently accepted prognoses for both pure adenoacanthoma and adenocarcinoma of the endometrium may have to be revised. (20 refs.)

77-0431 The Occurrence of Squamous Metaplasia as a Precursor of Squamous Cell Carcinoma of the Endometrium. (Eng.) Seltzer, V. L. (60 Sutton Place South, New York, NY 10022) Klein, M.; Beckman, E. M. *Obstet Gynecol* 49(1): 34s-37s; 1977.

A case of primary squamous cell carcinoma of the endometrium in a 55-yr-old woman is reported. The patient was admitted with a chief complaint of postmenopausal bleeding of 6 mo duration. Pelvic examination revealed normal female external genitalia and an atrophic vaginal mucosa. The cervix was nulliparous, and there was a dark red mucous discharge coming from the os. A fractional dilatation and curettage revealed poorly differentiated squamous cell carcinoma of the endometrium and a small submucous leiomyoma. A radical hysterectomy with bilateral pelvic lymph node dissections was performed. The specimen contained poorly differentiated squamous cell carcinoma of the endometrium arising in a focus of squamous metaplasia. The tumor had invaded 50% of the depth of the myometrium. The endometrium was otherwise inactive. The only abnormality of the cervix was a small endocervical leiomyoma. Both ovaries were atrophic. No tumor was found in 28 regional lymph nodes. The para-aortic nodes were palpated during surgery and were not enlarged. The patient had an uneventful postoperative course and has had no tumor recurrence during 19 mo of followup. This is the 20th documented case of primary squamous cell carcinoma of the endometrium. It is postulated that squamous metaplasia of the endometrium is a potentially pathologic process that may be a precursor to squamous cell carcinoma. (16 refs.)

- 77-0432 **AFP Synthesis in Teratocarcinoma: Immunopathological Studies of Yolk Sac Tumor.** (Eng.) Urano, Y.; Endo, Y.; Tsuchida, Y. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S. (New York: Academic Press, Inc.): pp. 131-137; 1976.

Six cases of teratoma tumors associated with elevated levels of afetoprotein (AFP) are presented. The localizations were sacrococcygeal, ovarian, suprasellar, mediastinal, and testicular. All the tumors had histological aspects of endodermal sinus tumor (yolk sac tumor) in pure or mixed form. AFP was found in the cytoplasm of tumor cells forming the lining of vitelline cysts as well as Schiller-Duval bodies and vacuolated meshwork. AFP was demonstrated on the ribosomes of the rough endoplasmic reticula by an electron microscopic peroxidase antibody method. Thus, synthesis of AFP was found to occur in the cytoplasm of the tumor cell itself and on the ribosomes of the rough endoplasmic reticula. (15 refs.)

- 77-0433 **Demonstration of Hormonal Sensitivity in Gynaecomastic Tissue by Thymidine Incorporation In Vitro.** (Eng.) Poulsen, H. S. (Inst. Cancer Res., Radiumstationen, Norrebrogade 44, DK-8000 Aarhus C, Denmark) *Acta Pathol Microbiol Scand [A]* 85(1): 19-24; 1977.

Gynaecomastic tissues from six patients were tested for testosterone and estrogen sensitivity, as measured by ^3H -thymidine incorporation in tissue fragments. There were two patients with bilateral gynecomastia (A, B), three with left-

sided gynecomastia (C, E, F), and one with right-sided gynecomastia (D). Compared with controls, cultures from five (A, C, D, E and F) out of the six patients showed a significantly higher thymidine uptake when cultivated with 10^{-6}M testosterone. There was no effect of estradiol or testosterone on the cultures from patient B. Thymidine uptake was not inhibited in any of the cultures. The biopsy specimens were of the appearance typical of gynecomastia. Histological examinations of the cultures demonstrated that the tissue was, in general, well-preserved after 24 hr. The cultivated fragments showed the same morphology as the uncultivated preparations. If degenerative cytological abnormalities (pycnotic nuclei, necrosis, and vacuolization of the cytoplasm) were observed, they were not cell-type-specific. In conclusion, both estrogen and androgen may be involved in the development of gynecomastia, drug-induced gynecomastia is not only a direct effect of the drugs on the breast tissue but may be indirectly due to estrogen action, and estrogen sensitivity is similar for all gynecomastic patients. (27 refs.)

- 77-0434 **Adenoacanthoma of the Endometrium with Widespread Psammoma Bodies. Histological, Histochemical, and Ultrastructural Study.** (Fre.) Gloor, E. (Institut de Pathologie, Centre Hospitalier Universitaire Vaudois, CH 1011 Lausanne, Switzerland) Dessarzin, S.; Sadegh-ee, S.; Campiche, M. *Arch Anat Cytol Pathol* 24(6): 459-461; 1976.

An unusual case of adenocanthoma of the endometrium occurred in a 52-yr-old woman. A single episode of metrorrhagia prompted a curettage, which was followed 1 mo later by a total extended hysterectomy. The patient was in good health without gynecological symptoms 15 mo postoperatively. Macroscopic examination revealed a proliferative-phase endometrium with zones of adenomatous hyperplasia of variable degree. In the midst of the adenocarcinomatous areas, an adenoacanthoma-type epidermoid differentiation was evident. Scattered throughout the endometrium were spherical bodies (diameter, 10-30 μg) that resembled psammoma bodies, but they had a fibrillar structure and histochemical reaction typical of keratin. Accumulations of spherical bodies compressed the choroid and they were also observed in the uterine glands. The myometrium was not invaded. There were two glandular-type polyps at the base of the uterine cavity; they did not contain spherical bodies. The left ovary had a small, simple, serous cyst and a yellow body; otherwise, the ovaries, tubes, and omentum were free of pathology. Ultrastructurally, keratinization was evident in the presence of many cells that were completely or partially desiccated, with bundles of fibrils replacing the cytoplasm and the nucleus shrunken or absent. The cell transformation resembles that observed in benign cutaneous calcifying epithelioma of Malherbe. (10 refs.)

- 77-0435 **Leiomyomatosis Peritonealis Disseminata. Report of a Case and Review of the Literature.** (Eng.) Goldberg, M. F. (Dept. Obstetrics and Gynecology,

Virginia Commonwealth Univ., Health Sciences Div., Medical Coll. Virginia, 1200 Broad St., Richmond, VA 23298) Hurt, W. G.; Frable, W. J. *Obstet Gynecol* 49(1): 46s-52s; 1977.

A case of leiomyomatosis peritonealis disseminata (LPD) in a 37-yr-old black woman is reported. On bimanual examination, a firm, slightly tender uterus of 12 wk gestational size was palpated. In the right adnexal area, there was a firm 3.0-4.0-cm mass that was thought to be an ovary or possibly pedunculated leiomyoma. At surgery, the uterus exhibited several subserous leiomyomas < 1.0 cm in diameter. Of special interest was the finding of multiple round, firm, slightly irregular nodules, 1.0 to 5.0 cm in diameter, that seeded the peritoneum, omentum, mesentery, small and large bowel, and filled the cul-de-sac. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and appendectomy, with resection of as many of the larger masses from the peritoneum as practical, were performed. Examination at 6 wk after surgery and again at 10 mo revealed the patient to be in good health. Tissue examination of the surgical specimens revealed multiple leiomyomas of the omentum, mesentery, and sigmoid colon, several small subserous leiomyomas of the uterus, and a small leiomyoma of the left broad ligament. Microscopic sections from many areas of the leiomyomas demonstrated smooth muscle proliferation of varying cellularity. There were areas of hyaline degeneration and the typical whorl-like pattern of benign leiomyomas. Electron micrographs showed features found in smooth muscle cells. There was evidence for *in situ* leiomyomatosis and the early development of a leiomyoma in a vessel wall. This is the eighth reported case of LPD. Additional information is needed to clarify the hormonal relationships associated with the condition. (13 refs.)

77-0436 **The Management of Mature Teratoma of the Testicle.** (Eng.) Dunn, D. (Dept. Surgery, Univ. Minnesota, Minneapolis, MN 55455) Hertel, B.; Kennedy, B. J. *J Urol* 117(2): 259-261; 1977.

A case report of mature teratoma of the testis, which emphasizes the unpredictability and malignant potential of these tumors, is presented. It also represents the longest documented interval between diagnosis and metastases. A 19-yr-old man injured his left testicle while straddling a fence in 1957. After a short period of acute pain and swelling, the testicle gradually decreased somewhat but nevertheless, it remained noticeably enlarged. Upon hospitalization 5 yr later for unrelated causes, the enlargement was noted, and an inguinal orchiectomy was performed. The patient remained in good health until March 1975, when he presented with a 3-day history of left flank pain radiating to the lower abdomen. Roentgenograms showed a calcified 3-cm mass in the left paravertebral area. Left transabdominal radical lymphadenectomy yielded 20 teratocarcinomatous lymph nodes. Four months later, an anterior abdominal mass was noted. Vinblastine and bleomycin therapy was instituted, but the mass increased further. A biopsy showed pure embryonal cell

carcinoma without teratomatous elements. The literature was reviewed to evaluate the optimum mode of therapy for this tumor. The clinical features, pathology, treatment, and survival indicate that the mature teratoma can be a potentially malignant neoplasm. (20 refs.)

77-0437 **Mixed Testicular Tumor in Immunosuppressed Patient: Case Report.** (Eng.) Cabrera, R. C. (Dept. Radiotherapy, Box 1211, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203) Bohorquez, J. F.; Kinkhabwala, R.; Kountz, S. L. *J Urol* 116(6): 823-824; 1976.

The case of a mixed testicular tumor in an immunosuppressed 30-yr-old man is presented. The patient was hospitalized in January, 1975, because of a right testicular mass less than 2 mo in duration. History showed chronic renal failure secondary to chronic glomerulonephritis in April, 1974. Hemodialysis was begun 1 mo later, and in August he received a living related (father) renal allograft followed by radiation therapy to the graft because of mild rejection episodes immediately postoperatively. The patient received 150 R 6x every other day, as well as methylprednisolone sodium succinate and azathioprine *iv*. Both testes were normal on his first admission in August. The patient was rehospitalized twice for fluctuating fever and rising blood urea nitrogen and creatinine, with tenderness on the grafted area. He was treated each time with 250-500 mg methylprednisolone sodium succinate *iv*, 150 mg *po* azathioprine daily, and 90-210 mg *po* prednisone daily. In the interim, the patient was followed in the clinic and was taking imuran and prednisone daily. Three mo after the renal transplant, he noticed that the right testis was getting bigger. Physical examination revealed the right testis to be twice as large as the left testis, uniformly hard, and non-tender. On January 29, 1975, he underwent a right orchiectomy, which demonstrated seminoma with some teratomatous component. A lymphangiogram was non-revealing. The patient was treated with radiation to be followed by chemotherapy. The temporal relationship in the development of the tumor in the presence of immunosuppressants suggests the significance of the immunodefense mechanism in the control, growth, or development of the neoplasm. (3 refs.)

77-0438 **Scanning Electron Microscopy of Cells in the Lymph of the Human Thoracic Duct in Advanced Malignancies.** (Eng.) Dahlback, O. (Dept. Thoracic Surgery, Univ. Hosp., S-221 85 Lund, Sweden) Dencker, H.; Hakansson, C. H.; Lindberg, L. G.; von Mecklenburg, C. *Acta Radiol [Ther]* (Stockh) 15(6): 519-528; 1976.

Cells from the lymph of the thoracic duct were examined by electron microscopy in 30 patients (19 women, 1 man with mammary carcinoma; 3 men with carcinoma of the urinary bladder; 4 men and 2 women with pulmonary carcinoma, and 1 patient with malignant melanoma). The few malignant cells found came from patients with pulmonary carcinoma and mammary carcinoma with lung metastasis. A number of abnormal shapes of the RBC were observed that may have been

due to factors such as administered drugs or abnormal metabolites from the malignancy. The lymphocytes had no consistent pathologic shape, but seemed to serve as immunologically active cells against the malignant cells in the thoracic lymph. (21 refs.)

- 77-0439 Pulmonary Oncocytes in Prolonged Hyperoxia.** (Eng.) Bonikos, D. S. (Dept. Pathology and Oncology, Stanford Univ. Sch. Medicine, Stanford, CA 94305) Bensch, K. G.; Watt, T.; Northway, W. H. *Exp Mol Pathol* 26(1): 92-102; 1977.

The ultrastructure of pulmonary oncocytes experimentally induced in newborn mice exposed to prolonged hyperoxia was studied. In 30 separate experiments, 496 newborn C57BL/Ka mice were continuously exposed to humidified 100% oxygen at normal atmospheric pressure or to humidified air at a rate of 6 liters/min for 2, 3, 4, or 6 wk. Each newborn received an ip injection of 1 μ Ci 3 H-thymidine/g body wt 1 hr prior to sacrifice. Electron microscopy revealed oncocytes in the epithelial lining of the bronchi, bronchioli, and alveoli. The morphological progression of cells to true oncocytes is described. As early as 2 wk after continuous exposure, "early oncocytes" showing mitochondrial abnormalities were observed; by 3 wk, true oncocytes were noticeable. Between 4 and 6 wk, oncocytes with all of the typical features could be identified in the epithelial lining of both transitional and conductive airways. These oncocytes may be an accentuated type of compensatory mitochondrial hypertrophy caused by exhaustion of one or more of the mitochondrial enzymes, secondary to the hyperoxia. The possible relationship of these cells to oncocytoomas and neoplastic transformation is discussed. (40 refs.)

- 77-0440 Rare Forms of Metastatic Affection of the Pleura.** (Rus.) Romanychev, Y. A. (P. A. Gertsen Moscow Scientific Res. Inst. Oncology, Moscow, USSR) Pirogov, A. I.; Marmorshtein, S. Y. *Vestn Rentgenol Radiol* (5): 64-68; 1976.

Seventeen patients with metastases to the lungs with tumor nodes but no pleurisy, effusion, or accumulation of fluid were studied. These metastases derived from tumors of the lungs, mediastinum, ovaries, breast and thyroid gland as well as from malignant synovioma and renal cell carcinoma. It was difficult to distinguish between these metastases and mesothelioma of the pleura. (5 refs.)

- 77-0441 Mediastinal Choriocarcinoma in a Chromatin-Positive Boy.** (Eng.) Storm, P. B. (Univ. Iowa, Iowa City, IA) Fallon, B.; Bunge, R. G. *J Urol* 116(6): 838-840; 1976.

A case of primary mediastinal choriocarcinoma in a 16-yr-old chromatin-positive boy is reported. For 1 mo, the patient had

had frontal headaches, light-headedness, and increasing dyspnea on exertion associated with easy fatigability. Anemia and melena were observed, as well as a large mediastinal mass on chest x-ray. The x-ray was interpreted as showing a large hilar mass on the right side and scattered metastatic lung nodules. The presence of bilateral frontoparietal masses was suggested. A right anterior thoracotomy was performed with biopsy evidence of metastatic choriocarcinoma. Microscopically, there were sheets and nests of neoplastic cells invading the lung with large areas of hemorrhagic necrosis with cytotrophoblastic and syncytiotrophoblastic cells throughout. Urinary chorionic gonadotropins collected postoperatively measured 1,620,000 IU per 24 hr. Combined chemotherapy with vinblastine and bleomycin was begun 10 days postoperatively, associated initially with leukopenia and clinical deterioration with increasing liver enzymes, blood urea nitrogen, and upper gastrointestinal bleeding. Chemotherapy was stopped but was resumed after clinical stabilization. The patient was discharged but returned 13 days later with recent increase in lethargy associated with grand mal seizures. He died 24 hr later. Autopsy revealed a 10 x 7 x 5 cm, 320 g, well encapsulated, lobulated ovoid mass in the anterior mediastinum adherent to the right lung. It had a variegated interior with areas containing hair, cartilage, cystic spaces filled with clear mucus, and a few areas of focal necrosis. Microscopic diagnosis was teratoma with choriocarcinoma. Metastatic lesions were widespread in the lungs, liver, spleen, brain, kidneys and jejunum, all of which were pure choriocarcinoma. Cause of death was attributed to uncalled herniation and brainstem compression from generalized cerebral edema and multiple hemorrhagic metastases. The testicles were 2.2 cm long on the right side and 2 cm on the left side. There was tubular atrophy associated with Leydig cell hyperplasia. The patient is the twenty-third reported case of primary mediastinal choriocarcinoma. (15 refs.)

- 77-0442 Airway Malignancy in Poisonous Gas Workers.** (Eng.) Kurozumi, S. (Dept. Otorhinolaryngology, Hiroshima Univ. Sch. Medicine, Hiroshima, Japan) Harada, Y.; Sugimoto, Y.; Sasaki, H. *J Laryngol Otol* 91(3): 217-225; 1977.

Case histories are presented of four workers in a Japanese nitrogen mustard gas factory during World War II who subsequently developed malignant tumors of the respiratory tract. Two of the patients had tracheal cancers, one a laryngeal cancer, and one an uvular cancer. All of the tumors were excised, and sections were examined by electron microscopy. Squamous epithelial metaplasia of the bronchial mucous membrane near the malignancy and of the tracheal mucous membrane was found. Numerous secretory granules were seen over the tracheal epithelium. These findings suggest an increased secretion due to proliferation of the mucous glands and goblet cells. Irregularity in the arrangement and direction of the cilia of the tracheal mucous membrane was also observed. In workers from this factory who had acute exposures, regeneration of the mucous membrane was almost complete. In workers who had been subjected to the gas for

years, however, the injury to the tracheal mucous membrane was chronic, with a permanent effect on the mucosa. These findings support the hypothesis that metaplasia is the carcinogenic factor in respiratory tract cancer. (9 refs.)

77-0443 Short- and Long-Term Behavior of Pleural Effusion Cultures. Report of 200 Cases. (Fre.)

Mouriquand, J. (Laboratoire d'Histologie de la Faculte de Medecine de Grenoble, Domaine de la Merci, 38700 La Tronche, France) Mouriquand, C.; Petitpas, E.; Mermet, M. A.; Augusseau, S.; Paramelle, B. *Pathol Biol (Paris)* 25(1): 15-21; 1977.

In vitro cultures of pleural effusions from 200 patients with benign or malignant (45 metastases, 9 mesotheliomas, 7 malignant blood disorders, 19 lung cancer) pleural involvement were observed for 48 hr to 9 mo. Cells were cultured in Eagle's minimum essential medium fortified with L-glutamine and fetal calf serum plus insulin (5 µg/ml) penicillin (100 units/ml), and streptomycin (100 µg/ml). Once a continuous cell layer formed, the cells were subcultured for a max of 10 times. The cellular elements of the effusions had varied characteristics and varied survival. Lymphocytes hardly survived a week. Monocytes and macrophages continued to be recognizable and frequently affixed themselves to the glass of the culture tubes. Mesothelial cells did not form continuous layers, but long, thin cytoplasmic processes permitted intercellular contact. Intermingled were single or binucleated large polygonal cells without cytoplasmic processes. Not all the malignant epithelial cells grew well in culture. When growth succeeded, the malignant cells had a tendency to grow in clusters that would break off into the culture medium. In effusions from mesothelial hyperplasia (6 infectious, 5 cardiac, 5 pulmonary infarction, 2 tubercular), the mesothelial cells tended to form clumps similar to those of the malignant epithelial cells. Discrepancies in diagnoses of malignancy by conventional cytology and cell culture occurred in 13 cases. In 6 cases positive for malignant cells using conventional cytology, the cell culture was negative; the opposite was true in 7 cases. (16 refs.)

77-0444 Ultrastructural Alterations of Apud Cells During Nitrosamine-Induced Lung Carcinogenesis. (Eng.)

Reznick-Schuller, H. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany) *J Pathol* 121(21): 79-82; 1977.

Groups of Syrian golden hamsters were treated with diethylnitrosamine (DEN; 17.8 mg/kg/wk × 2, sc, for life) and N-dibutyl nitrosamine (DBN; 351 mg/kg/wk, sc, for life) to see if they would produce comparable degrees of Apud-cell (amine precursor uptake and decarboxylase activity) proliferation and, also, to study the sequential ultrastructural alterations of this cell type during pulmonary carcinogenesis. After 2-3 wk, both DBN- and DEN-treated animals exhibited

hyperplastic areas in the segmental bronchi and peripheral bronchioles, which were composed of Apud cells. After 5-6 wk of treatment with DEN and 8-9 wk with DBN, several Apud cells contained delicate filaments in their cytoplasm. During the following week, these filament-bearing Apud cells increased in number, as did the number of filaments per cell. A tendency to form bundlelike structures was also seen. After 18-20 wk of DEN treatment, the Apud cells demonstrated pronounced perinuclear bundles of cytoplasmic filaments, which were also seen in DBN-treated hamsters after 16 wk. These cells exhibited a simultaneous decrease in their number of neurosecretory granules, and in some cases only one granule per cell was seen. Untreated control animals demonstrated no Apud cells in their bronchial lining. It still must be determined whether these alterations are specifically nitrosamine-induced and what their exact role is in carcinogenesis. (15 refs.)

77-0445 Congenital Mesenchymal Tumour of the Lung. (Eng.)

Haller, J. O. (Dept. Radiology, Downstate Medical Center, State Univ. New York, 450 Clarkson Ave., Brooklyn, NY 11203) Kauffman, S. L.; Kassner, E. G. *Br J Radiol* 50(591): 217-219; 1977.

A full-term baby girl with massive generalized edema, severe respiratory distress, and radiograph evidence of a large mass in the left hemithorax died 8 hr after birth. Findings at autopsy showed the left lower lobe of the lung to be almost totally replaced by a dark red tumor measuring 5.5 × 4.0 cm and displacement of the heart to the right. The final pathological diagnosis was congenital mesenchymal tumor of the lung with leiomyomatous elements. A preductal coarctation of the aorta may also have contributed to the infant's severe perinatal distress. (9 refs.)

77-0446 Large Spindle Cell Variant of Peripheral Bronchial Carcinoid Tumor. (Eng.)

Churg, A. (Dept. Pathology, Univ. Chicago, 950 E. 59th St., Chicago, IL 60637) *Arch Pathol Lab Med* 101(4): 216-218; 1977.

A 37-yr-old woman underwent a lobectomy for a coin lesion of the left lower lobes that was diagnosed at the time as a benign tumor. Electron microscopic examination of the tumor showed it to be composed almost entirely of large spindle cells with an abundant eosinophilic cytoplasm. The typical polygonal or small spindle cells of the type commonly seen in carcinoids were not observed. When comparison was made with a peripheral carcinoid tumor of the small spindle cell type it was observed that the nuclear shape and chromatin pattern were similar, but the nuclei of the "control" tumor were slightly smaller, with a much less abundant cytoplasm that stained poorly. The max cell length of the control tumor was < 25 µm, whereas in the tumor under study some cells measured at least 50 µm in length. The unusual features of this carcinoid tumor are discussed. (8 refs.)

- 77-0447 Double and Multiple Bronchial Tumors.** (Ger.) Geroulanos, S. (Chirurgische Universitätsklinik A, Kantonsspital, CH-8091 Zurich, Switzerland) Roenspies, U.; Marxen, F.; Otto, R.; Hahnloser, P. *Helv Chir Acta* 43(5/6): 609-613; 1976.

Seven dual tumors of the tracheobronchial tree were found among 1,908 malignant and 77 benign bronchial tumors. Two of these seven patients had combinations of a malignant and a benign bronchial tumor; the other five had two or more benign bronchial tumors. A multiple, synchronous hamartoma was found in one case, a solid adenoma followed 8 yr later by a contralateral, histiocytomalike tumor in another. Pulmonary carcinoid-type adenomas were found in three cases; they were synchronous and homolateral in two, contralateral and developing at a 1-yr interval in the third. (16 refs.)

- 77-0448 Hepatocellular Carcinoma in Association with Androgen Therapy.** (Eng.) Goodman, M. A. (Univ. Dept. Surgery, Royal Perth Hosp., Box X2213, G.P.O. Perth, W. Australia) *Med J Aust* 1: 220-221; 1977.

A 25-yr-old man presented with fever, sweating, and pleuritic left hypochondrial pain. At the age of 11 yr he had undergone bilateral orchidopexy. At age 20, he was examined for hypogonadism, for which he was prescribed methyltestosterone (25 mg twice daily) for 5 yr. Liver scan showed hepatomegaly; at laparotomy, two large necrotic liver masses were found in the left liver lobe and one in the right. Histology disclosed a diagnosis of well-differentiated hepatocellular carcinoma. The relationship between steroid therapy and hepatocellular tumors is discussed. (13 refs.)

- 77-0449 Hepatic Adenoma and Oral Contraceptives.** (Dut.) Grijm, R. (Kliniek voor Inwendige Ziekten, Wilhelmina Gasthuis, Amsterdam, Netherlands) Agnani, D. M.; Tytgat, G. N. *Ned Tijdschr Geneesk* 120(50): 2221-2223; 1976.

The case history of a 26-yr-old woman with hepatomegaly resulting from two large, highly vascularized tumors in the right and left lobes is presented. She had used oral contraceptives for the past 5 yr. The diagnosis was bilateral adenoma of the liver. (16 refs.)

- 77-0450 Benign Liver Tumor After Oral Contraception.** (Fre.) Letoublon, C. (Pavillon Brenier 1, Chirurgie Generale, Clinique Obstetricale et Gynecologique, C.H.U. de Grenoble, F 38700 La Tronche, France) Champetier, J.; Benbassa, A.; Pasquier, D. *Nouv Presse Med* 5(44): 3014; 1976.

A liver adenohamartoma in a 33-yr-old woman who had been

taking the oral contraceptive Ovariostat (Lynestrol, 2.5 mg; mestranol, 0.075 mg) for 7 yr is reported. Laparotomy revealed a large tumor in the right lobe of the liver, surrounded by a band of normal liver tissue. Histological diagnosis of the tumor after excision was adenohamartoma altered by hemorrhage and necrosis. A total of 92 cases of benign tumors of the liver associated with oral contraceptives have been reported in the literature. Duration of treatment and the type of estrogen in the contraceptive appear to influence tumor incidence. (6 refs.)

- 77-0451 Liver Changes Following Long-Term Use of Anabolic Steroids and Oral Contraceptives.** (Dut.) Bakker, K. (Endocrinologische afdeling, Kliniek voor Inwendige Geneeskunde, Academisch Ziekenhuis, Groningen, Netherlands) Brouwers, T. M.; Houthoff, H. J.; Postma, A. *Ned Tijdschr Geneesk* 120(50): 2214-2220; 1976.

Liver lesions resulting from the protracted use of anabolic steroids and oral contraceptives are discussed. The postmortem examination of two patients who had used anabolic steroids indicated that one of the patients had multiple liver cell tumors and peliosis hepatitis. In two patients who had used oral contraceptives, liver scans indicated decreased uptake in the left lobe; this disappeared after discontinuation of the treatment in one. The other patient had a hepatic tumor with focal nodular hyperplasia. A review of the literature is presented; the difficulties in the histological diagnosis of these lesions and their therapeutic consequences are discussed. (38 refs.)

- 77-0452 Hepatocellular Carcinoma. A Possible Complication of Oral Contraceptive Steroids.** (Eng.) Schmidt, G. (Gardens Medical Centre, 50 Nelson Road, Box Hill, Vic. 3128, Australia) *Med J Aust* 1: 215-217; 1977.

A 32-yr-old patient developed a primary hepatocellular carcinoma after taking an oral contraceptive steroid preparation for 4 yr. After resection of the tumor, and resumption of the birth control pill, a recurrent hepatocellular carcinoma developed. The oral contraceptives were withdrawn, and a liver scan 6 mo later showed no increase in the size of the lesion. The risk of this tumor in women taking birth control pills is probably extremely small and appears to be related to the duration of ingestion of the drug and to the amount of estrogen present in the preparation used. (6 refs.)

- 77-0453 Liver Tumor and Oral Contraceptives. Report of a Case and Literature Review.** (Ger.) Kamber, J. (Kantonales Institut für Pathologie, Rheinstrasse 37, CH-4410 Liestal, Switzerland) Michot, F.; Villiger, K. J. *Schweiz Med Wochenschr* 107(1): 17-22; 1977.

The case history of a 33-yr-old woman with a hamartoma

(focal nodular hyperplasia) of the right lobe of the liver is presented. She presented with signs of chronic cholecystitis and cholelithiasis. She had been treated with radiation and chemotherapy for Hodgkin's disease at the age of 20. She had been on oral contraceptives for 2 yr. Approx 70 cases of benign liver tumors occurring in women on oral contraceptives have been reported in the literature. More than one-third were found because of life-threatening intra-abdominal bleeding due to tumor rupture. A causative relationship between hepatic tumors and the use of oral contraceptives is suggested. (43 refs.)

77-0454 Invasion of the Duodenum by Carcinoma of the Stomach. (Eng.) Koehler, R. E. (Mallinckrodt Inst. Radiology, Washington Univ. Sch. Medicine, Saint Louis, MO 63110) Hanelin, L. G.; Laing, F. C.; Montgomery, C. K.; Margulis, A. R. *Am J Roentgenol Radium Ther Nucl Med* 128(2): 201-205; 1977.

Invasion of the duodenum by stomach carcinoma was studied in 111 patients, 41 women and 70 men (19 to 91 yr old, av, 65). There was histologic documentation of invasion of the duodenal wall in 20 cases. Tumor cells were found predominantly in the muscular and submucosal layers of the duodenum, but mucosal invasion was occasionally observed. The radiographic features of the invasion were analyzed in 11 cases. In all 11, abnormality in the duodenal bulb was contiguous with abnormalities in the pylorus and gastric antrum. Distortion of the contour of the duodenal bulb varied from irregularity involving only the proximal portion of the bulb in four cases to deformity of the major portion of the bulb in three others. In two cases, a nodule arose from the duodenal surface of the pylorus and protruded into the proximal duodenum. In one patient, a lobulated antral mass extended through the pylorus into the duodenum. In another patient, the duodenum was narrowed as far distally as the ampulla of Vater. Of 19 patients undergoing gastric resection for lymphoma, 3 had microscopic evidence of invasion of the duodenum, and in 1 of these the duodenal involvement was evident radiographically and grossly. Radiographic abnormalities of the duodenum in this case were similar to those seen in one of the patients with transpyloric extension of gastric carcinoma. Eighteen of the 19 patients had no evidence of gross duodenal involvement. Carcinoma seems to be the likely diagnosis in a patient with duodenal involvement by an antral tumor. (16 refs.)

77-0455 The Localization of Precancerous Changes and Carcinoma After Previous Gastric Operation for Benign Condition. (Eng.) Hammar, E. (Dept. Pathology, Univ. Hosp., S-221 85 Lund, Sweden) *Acta Pathol Microbiol Scand [A]* 84(6): 495-507; 1976.

The localization of precancerous changes and carcinoma following a previous gastric operation for a benign condition was evaluated in 65 patients: 9 with precancerous changes

(Group I), 22 with early gastric carcinoma (Group II), and 34 with infiltrative cancers (Group III), all discovered upon reoperation. Reexamination of 35 gastric specimens obtained at the primary operation for ulcer disease demonstrated no precancerous changes or cancer. In Groups I and II, 20/26 patients had been given a Billroth II in which the efferent loop was situated on the left side. In Group III, this procedure had been utilized in 17/30 cases. The site of the primary ulcer in the groups was the duodenum (31 cases), the pylorus (3 cases), and the stomach (17 cases). Av age at first and second operation was 43.0 and 58.8 yr (Group I), 40.2 and 63.6 yr (Group II), and 46.9 and 67.7 yr (Group III). There were 27 intestinal type and 29 diffuse gastric type cancers. Twenty Group III patients died of diffuse gastric cancer and 5 died of cancer of the intestinal type. Infiltrative cancer of the gastric remnant was seen in the cardiac region (3 cases), the entire remnant (6 cases), and adjacent to the anastomosis (25 cases). In Group I, 5/6 patients had precancerous changes situated adjacent to the efferent limb. In Group II, 7/20 patients had diagonally situated carcinoma in situ. In eight cases, cancer was seen only at the efferent limb. In Group III, 2/23 patients had diagonally situated cancers. Fifteen cases had cancer only at the efferent limb. In the remaining six cases, it was not known which limb was efferent or afferent. Among 49 cases with anastomosis, it was possible to select 37 patients demonstrating changes at the efferent loop extending mainly toward the posterior gastric wall. In 10 of these cases, additional changes were diagonally situated toward the afferent loop cephalically within the jejunum. In 4/5 patients with Billroth I, the changes were situated within the anastomosis at the minor curvature. Further investigations are needed to determine more exactly the site of carcinogenesis in operated stomachs and the factors influencing its occurrence. (47 refs.)

77-0456 Pure Red-Cell Aplasia. Associated with Adenocarcinoma of Stomach. (Eng.) Gajwani, B. (Dept. Medicine, Wilson Memorial Hosp., Johnson City, NY) *NY State J Med* 76(13): 2177-2179; 1976.

The case history of a 76-yr-old woman with pure red-cell aplasia (PRCA) associated with adenocarcinoma of the stomach is presented. She had a long history of arthritis and had been taking analgesics and small doses of prednisone (5 to 10 mg/day). Gastroscopy and biopsy indicated a well-differentiated adenocarcinoma. After undergoing subtotal gastrectomy, she remained in complete remission for over 2 yr but developed a relapse of PRCA. A liver scan confirmed metastases. This is the fifth such case of simultaneous occurrence of carcinoma and PRCA in literature. (17 refs.)

77-0457 A Modified Leukocyte Adherence Inhibition Test in the Laboratory Investigation of Gastrointestinal Cancer. (Eng.) Rutherford, J. C. (Repatriation General Hosp, Greenslopes, Brisbane, Queensland, Australia) Walters, B. A.; Cavaye, G.; Halliday, W. J. *Int J Can-*

cer 19(1): 43-48; 1977.

Leukocyte adherence inhibition is a technique based on the observation that addition of an appropriate tumor extract reduces the ability of blood leukocytes from a cancer patient to adhere to glass. It was used to test the monocytes of 60 hospital patients with gastrointestinal symptoms for inhibition of adherence by extracts of colon, pancreas, and stomach tumors. Prior to clinical diagnosis, groups of patients with adenocarcinoma of the rectum (11 patients), carcinoma of the stomach (3), and adenocarcinoma of the stomach (6) were clearly distinguished from each other and from patients with nonmalignant diseases or with neoplasms of different histological types. (24 refs.)

- 77-0458 **Blood Group Determinants in Malignancy Foreign to Host.** (Eng.) Levine, P. In: *Oncogenetic Developmental Gene Expression. Papers presented at a conference sponsored by the International Research Group for Carcinoembryonic Proteins, and held at San Diego, May 29-June 1, 1976.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 485-491; 1976.

Sugar determinants, foreign to the genotype of the host, were found in adenocarcinomas during studies of the carbohydrate chain of the blood group glycosphingolipids of red blood cells. The case of a 66-yr-old woman first presented in 1951 is reviewed and discussed in light of recent discoveries. The woman was suffering from a gastric adenocarcinoma. Her genotype was pp, but her serum contained anti-P₁P₂Pk, 1:8. Absorption tests with the resected adenocarcinoma showed that the cancer failed to absorb any of the isoantibodies except its own anti-P₁P₂Pk. The adenocarcinoma contained a determinant of the P₁P₂Pk complex, which was foreign to the host that could transmit only gene p. The patient survived for 22 yr following subtotal gastrectomy without recurrence of the disease. The long survival may be associated with the high titer (1:512) of anti-P₁P₂Pk, which was present before the operation. The cytotoxicity of this complex was due to the presence of anti-P₁, specific for the fifth terminal galactose present exclusively in the adenocarcinoma. In anticipation of the more frequent O to A or the O to B mutation with adenocarcinoma, specific immunotherapy lies in the deliberate isoimmunization with small quantities of incompatible A₁ RBC to induce specific cytotoxicity directed against the fifth sugar in the chain. (9 refs.)

- 77-0459 **Early Gastric Cancer.** (Eng.) Johansen, A. A. (No affiliation given) *Curr Top Pathol* 63: 1-47; 1976.

The author's experience with 56 cases of early gastric cancer during the last 10 yr is reported. The average age of men was 68.6 yr and of women 65.5 yr, and the ratio of men to women was 1.8:1. The 64 lesions were divided into six groups according to their largest diameter. More than half had a max diameter

≤ 2 cm. Among tumors > 4 cm, five were ulcer cancers and two were type I papillomatous tumors. There was nearly a direct correlation between tumor size and degree of penetration. Practically all tumors were in the pyloric or intermediary zones. Almost no lesions were found in the body mucosa. In two cases, a relatively large number of parietal cells was revealed distal to the tumor, but they were observed together with many pseudopyloric glands. Eleven lesions extended into the body mucosa, where they were limited to the foveolar zone, but all had originated from the intermediary mucosa. Among the 56 resection specimens, 7 demonstrated multifocal lesions. In one case, three protruded type I carcinomas were found together with a pyloric adenoma showing severe precancerous changes. None of the intramucosal carcinomas showed lymph node metastases. Three submucosal carcinomas had one lymph node each with metastasis. The lymph node capsules were not pervaded. One of the patients died without metastases. The two others have survived for 4 and 8 yr. Among the 56 patients, 29 are alive and well. The longest period of survival is 10 yr, 9 mo. (146 refs.)

- 77-0460 **Hereditary Polyposis of the Colon: Experience with 19 Cases.** (Eng.) Raman, P. G. (Undergraduate Medical Hostel, Rewa, Madhya Pradesh, India) Kutteruf, G. C.; Veidenheimer, M. C.; Whitcomb, F. F. *Lahey Clin Found Bull* 26(1): 1-10; 1977.

Nineteen cases of hereditary polyposis of the colon seen at the Lahey Clinic Foundation between 1957 and 1974 are reviewed. Of these patients, 17 had familial polyposis and 2 had Gardner's syndrome, diseases associated with a high incidence of colonic malignancy. The patients ranged in age from 10.5 to 63 yr. Although soft tissue tumors and osteomas found in Gardner's syndrome patients rarely have malignant potential, these patients had a striking predilection for carcinoma of the pancreas and duodenum. Of the two cases described, one of them, a 41-yr-old woman, had carcinoma of the cecum at the time of diagnosis. All but 2/17 with familial polyposis had total colonic disease. Five of these patients had unsuspected carcinoma discovered at the time of operation, four of these developed carcinoma of the rectal stump, and one eventually died of ovarian carcinoma. All patients were treated initially with colectomy and ileoproctostomy, with careful postoperative follow-up and fulguration of recurrent polyps except for two lost to follow-up. Estimates indicate that as many as 50% of patients with familial polyposis may develop infiltrating colonic carcinoma by the age of 30, whereas the average age at development of carcinoma in Gardner's syndrome is 40. Except for extracolonic manifestations, symptoms found in both types of patients were similar. (31 refs.)

- 77-0461 **Stromal Invasion of Cancer in Pedunculated Adenomatous Colorectal Polyps.** (Eng.) Okike, N. (Section Publications, Mayo Clinic, Rochester, MN 55901) Weiland, L. H.; Anderson, M. J.; Adson, M. A. *Arch Surg* 112(4): 527-530; 1977.

Fifty-three patients were treated for pedunculated adenomatous colorectal polyps that contained foci of invasive carcinoma confined to the stroma. The age of the patients varied from 30 to > 80 yr, with nearly 75% between 50 and 70. Almost two-thirds of the polyps were > 1.5 cm in diameter. The sigmoid (31 cases) and rectum (12 cases) were the predominant sites of involvement, followed by the descending colon (8), ascending colon (1), and transverse colon (1). Treatment consisted of local excision of lesions in 24 patients, 13 endoscopically and 11 by transabdominal polypectomy. Resection and regional lymphadenectomy were performed in 27 patients (24 of these had colonic lesions and 3, low rectal lesions treated by abdominoperineal resection). Lymph nodes draining the 26 lesions treated by local excision were neither removed nor examined histologically. Examination of the 93 lymph nodes that had been removed with the resected specimen from 27 patients revealed no evidence of metastases. Local removal of lesions without regional lymphadenectomy is deemed an adequate treatment. (3 refs.)

77-0462 Experimental Carcinoma in the Rabbit Urinary Bladder. (Ger.) Gericke, D. (Hoechst AG, Frankfurt/Main, W. Germany) Hazrmann, R.; Bichler, K. *H. Naturwissenschaften* 64(1): 46-47; 1977.

The possibility of short-term transplantation of Brown-Pearce carcinoma confined to the urinary bladder for therapeutic experiments was studied in adult rabbits. Four animals (group 1) received 1 ml tumor cell suspension into one testicle. The take rate was 75%, and the animals developed widespread metastases in almost all organs. Another four animals (group 2) received 1 ml tumor cell suspension sc in the nape. The take rate was 25%, and there were only a few metastases. The survival was 4-6 wk in both groups. In group 3 (10 animals) the tumor cells were injected into the submucosa of the bladder, and in group 4 (12 animals) the bladder mucosa was sacrificed before tumor cell transplantation into the submucosa. The take was 100% in both groups. The survival was about 5 wk in group 3, 3-4 wk in group 4. Peritoneal metastases were found in group 3, but there were only paraaortic metastases in group 4. The latency appeared to become shorter over the consecutive passages. The findings indicate the possibility of inducing bladder tumors within 3 wk in rabbits by transplantation of Brown-Pearce carcinoma. (12 refs.)

77-0463 Familial Profile of Transitional Cell Carcinoma. (Eng.) Sharma, S. K. (Dept. Urology, Postgraduate Inst. Medical Education and Res., Chandigarh, India) Bapna, B. C.; Singh, S. M. *Br J Urol* 48(6): 442; 1976.

Transitional cell carcinoma was observed in two families in two generations. In the first family, it occurred in a father and his only son. The father (83 yr old) was hospitalized with complaints of dysuria, frequency of urination, and hematuria of 2.5 mo duration. There was delayed excretion on the right side and a filling defect on the right lateral wall of the bladder.

Cystoscopy showed an extensive growth. The histopathology was transitional cell carcinoma Grade III. His 58-yr-old son had an open transvesical excision of a bladder tumor in 1964. The histopathology was reported as Grade II transitional cell carcinoma. This was irradiated, but the patient developed hematuria requiring transurethral resection 6 mo later and again in February 1972. In September 1973, histopathology demonstrated poorly differentiated Grade III transitional cell carcinoma with squamous metaplasia. His three children are alive and well. In the second family, transitional cell carcinoma was recorded in two brothers; two other brothers and three sisters were asymptomatic. A 53-yr-old man presented in January 1972 with painless hematuria of 2 mo duration. There was a poorly functioning left kidney and a large filling defect in the left half of the bladder. The patient had transurethral resection and radiotherapy. The histopathology was Grade I. He had a recurrence in the first 6 mo, but later on he was recurrence-free. His 56-yr-old brother had painless hematuria in June 1972. There was a filling defect in the right renal pelvis. Nephroureterectomy with excision of a cuff of the bladder was done. The histopathology was transitional cell carcinoma. He was tumor-free in the subsequent follow-up. The mode of transmission in these two families appears to be consistent with an autosomal dominant trait. (2 refs.)

77-0464 Spectrum of Ultrastructural Patterns of Renal Cell Adenocarcinoma. (Eng.) Sun, C. N. (Dept. Urology, Univ. Arkansas Coll. Medicine, 4301 West Markham, Little Rock, AR 72201) Bissada, N. K.; White, H. J.; Redman, J. F. *Urology* 9(2): 195-200; 1977.

The ultrastructure of renal cell carcinoma was studied in six patients. A 50-yr-old man was found to have a right renal mass on hypertensive excretory urography. Arteriography demonstrated a 15-cm vascular mass occupying the lower pole of the right kidney, with discrete separation of the mass from the remainder of the kidney. This case demonstrated the classic features of granular cell carcinoma with numerous mitochondria and cell organelles. Another 50-yr-old man presented with low back pain due to an osteolytic bone lesion in the fifth lumbar vertebra. Investigations revealed a left renal tumor. Light microscopy showed a clear cell carcinoma arranged in sheets with a rather uniform pattern. A 54-yr-old man was admitted with an episode of gross, painless hematuria just prior to admission. Excretory urography and arteriography demonstrated a right renal tumor. Light microscopy demonstrated a clear cell carcinoma arranged in tubular formation. The second and third cases illustrate the classic patterns of clear cell carcinoma with greatly reduced endoplasmic reticulum, Golgi, and mitochondria, but abundant lipid droplets and glycogen granules. The last three cases represent intermediate patterns: a 54-yr-old man with a 10- x 10-cm calcified vascular mass occupying the upper pole of the right kidney (clear cell carcinoma); a 58-yr-old man with a 12- x 7-cm necrotic tumor having a variegated appearance; and a 49-yr-old man with a poorly vascularized mass in the upper pole of the left kidney (papillary adenocarcinoma). Interesting findings were the presence of basement membranes in the

last case and of connective-tissue banded structures in the third. (11 refs.)

- 77-0465 The Role of Urine in the Etiology of Cancer of the Urinary Bladder.** (Eng.) Parkash, O. (IIInd Surgery Dept., Wilhelminen Hosp., A-1171 Vienna, Austria) *Urol Int* 31(5): 343-348; 1976.

The site-frequency distribution of carcinomas relative to the upper and lower hemispheres of the urinary bladder was determined for 188 cases (both sexes) observed in one hospital during 1962-1971. Only 36 (19%) of these carcinomas occurred in the upper hemisphere, but 152 (81%) occurred in the lower hemisphere. From these results from literature cases, it is concluded that contact with urine containing carcinogens is the main factor in the etiology of bladder carcinoma. The time of contact with the mucosa (due to retention of urine over prolonged periods) and the concentration of carcinogens in the urine determine the different rates of occurrence in different parts of the bladder. Prolonged forced retention of the urine should, therefore, be avoided. (14 refs.)

- 77-0466 Nephrogenic Adenoma: A Form of Adenomatous Metaplasia of the Bladder. A Clinical and Electron Microscopical Study.** (Eng.) Molland, E. A. (Dept. Morbid Anatomy, London Hosp., London, England) Trott, P. A.; Paris, A. M.; Blandy, J. P. *Br J Urol* 48(6): 453-462; 1976.

A clinical and electron microscopic study of three cases of nephrogenic adenoma is presented. After fruitless attempts to provide relief to a 36-yr-old man by antibiotics and antispasmodics, subtotal cystectomy, in which 0.5 cm of bladder was left around the internal meatus, was performed. Both ureters were divided at the midpelvic level and implanted by Wallace's method into the tail of an isolated segment. By 6 wk, the patient had good control, without frequency or pain. The bladder of a 34-yr-old man was removed down to the internal meatus and replaced with an ileocecectoplasty segment, the ureters being anastomosed to the tail of the ileum. Recovery was uneventful, and 2 mo later he was without symptoms. In the third patient, a 41-yr-old man, cystectomy was performed because of the possibility of a premalignant condition. During the operation, carcinoma was discovered. Accordingly, a radical node dissection and en-bloc removal of the prostate and vesicles were carried out. His postoperative progress was uneventful. In both the subtotal cystectomy specimens of the first two cases, the mucosal surface was coarsely granular with reddish brown papillary lesions. There were papillary and polypoid areas with numerous glands lined by simple columnar epithelium extending down into the lamina propria in the first case and communicating with the surface epithelium in the second. The latter was replaced by simple columnar epithelium, but there was also some squamous metaplasia in the first case. The mucosa of the third case had reddish brown granular areas extending from the

region of the trigone to each lateral wall, with smooth surfaced polypoid areas in between. There was the typical appearance of adenomatous metaplasia adjacent to poorly differentiated adenocarcinoma secreting abundant mucus. Some of the cystic glands in the foci of adenomatous metaplasia were lined by atypical cells, and the surface epithelium that was lined by simple columnar epithelium also contained foci of atypical mucus-secreting cells. (15 refs.)

- 77-0467 Klinefelter's Syndrome and Bladder Cancer.** (Eng.) Fujita, K. (Urological Div., Saku Central Hosp., Minamisaku Usuda, Nagano, Japan) *J Urol* 116(6): 836-837; 1976.

A patient with Klinefelter's syndrome who also had transitional cell carcinoma of the bladder is described. A 41-yr-old man was hospitalized because of urethral pain and bleeding after urination. His mother died of colon cancer, and his father died of gastric cancer. He had three brothers and three sisters. The eldest brother, who died in an accident, had no children during his married life of more than 20 yr. A sister had sponge kidney. The patient weighed 88.5 kg and was 177.5 cm tall. Pubic hair was scanty, and both testes were rudimentary. Microscopic examination demonstrated WBC and RBC in the urine. One mo later, although the bladder symptoms and pyuria had disappeared, microscopic hematuria continued. A scout excretory urogram revealed a spherical defect 2 cm in diameter in the bladder near the left ureteral orifice. Urine cytology showed Class 5 malignancy. Cystoscopic examination revealed a broad-based neoplasm with neighboring scattered hyperemic areas of cancerous or precancerous changes. A cytogenetic study indicated mosaicism of 47XXY/46XY, with a proportion of 90/10%. Drumstick and sex chromatin patterns confirmed this finding. In order to provoke an immunologic reaction to the neoplasm, the patient was treated by hydrostatic pressure therapy. The remaining tumors were resected transurethrally. Convalescence was uneventful, and the patient was discharged from the hospital. The removed specimen revealed Grade 3-4 transitional cell carcinoma. The abrasion of the cancer cells and the presence of multiple lymph follicles in the lamina propria were thought to be the effects of hydrostatic pressure therapy. It is proposed that aneuploidy and neoplasm in the same family may have been caused by an inherited chromosomal instability rather than coincidence. (10 refs.)

- 77-0468 Carcinoma of the Bladder with Azathioprine Therapy.** (Eng.) Scharf, J. (Dept. Rheumatology, Rambam Univ. Hosp., Aba Khoushy Sch. Medicine Haifa, Israel) Nahir, M.; Eidelman, S.; Jacobs, R.; Levin, D. *JAMA* 237(2): 152; 1977.

The cases of two patients are reported in whom bladder tumors developed while they were receiving azathioprine. A 66-yr-old man with a history of ulcerative colitis since the age of 42 yr was treated with salicylazosulfapyridine and predni-

one. Because a severe exacerbation in 1967 could not be suppressed by prednisone, azathioprine (Imuran) therapy was instituted (2.5 mg/kg/day for 3 yr and then 1.5 mg/kg/day for 3 yr). A remission was achieved, and prednisone therapy was tapered off and discontinued 1 yr later. During the 6 yr of azathioprine treatment, the colitis was under control. In 1973, after massive hematuria, a grade 3 transitional cell carcinoma of the bladder was diagnosed and partially resected. The patient died 9 mo later from widespread metastases. A 67-yr-old woman had ulcerative colitis since the age of 43 yr. The clinical course had been one of chronic, continuous activity. Because she did not respond to treatment with salicylazosulfapyridine, a prednisone regimen was begun; her illness was then under control for 4 yr. During this time, however, severe osteoporosis developed, so that in January 1969, azathioprine therapy was started (2.5 mg/kg/day for 2 yr and then 1.5 mg/kg/day for 1.5 yr). The prednisone therapy was discontinued 8 mo later, and the colitis was under control. In 1972, a transitional cell carcinoma of the bladder was diagnosed and resected. The suppression of cytotoxic antibodies by prolonged immunosuppressive therapy may be instrumental in the development of urinary bladder carcinoma. (3 refs.)

77-0469 Squamous Metaplasia and Invasive Epidermoid Carcinoma of Bladder. (Eng.) Walts, A. E. (Div. Anatomic Pathology, Cedar-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048) *Urology* 9(3): 317-320; 1977.

A 29-yr-old woman was admitted for evaluation of recurrent irritative dysuria, left flank pain, and recurrent urinary tract infections. Her medical history included a vaginal hysterectomy for epidermoid carcinoma in situ of the cervix and rheumatoid arthritis. Cytoscopic examination revealed a large, necrotic tumor that occupied most of the anterosuperior bladder wall. At surgery, a tumor was found extending directly into the left obturator fossa. The pathologic report was a large, exophytic, keratinizing epidermoid carcinoma that deeply infiltrated the bladder wall. Close follow-up is suggested for young women with dysuria and chronic urinary infections, especially those with a long history of squamous metaplasia and/or leukoplakia. (15 refs.)

77-0470 Hypernephroma in Two Brothers. (Eng.) Lyons, A. R. (Northern Ireland Radiotherapy Centre, Belfast, Ireland) Logan, H.; Johnston, G. W. *Br Med J* 1(6064): 816-817; 1977.

The cases of two brothers with renal cell carcinoma are presented. The 53-yr-old brother was first seen in March 1974 with bilateral inguinal hernias and rectal bleeding. He returned with further rectal bleeding in December 1974, and routine examination demonstrated a large tumor mass in the left kidney. At operation, an 11-cm-diameter renal cell carcinoma was removed. In November 1975, the patient sustained a subcapital fracture of the left femur. At operation,

the upper end of the femur was infiltrated with secondary renal cell carcinoma. His condition gradually deteriorated, and he died on July 27, 1976. The 59-yr-old brother was first seen in November 1975 with rectal bleeding. Two mo later, he developed severe pain in the left kidney, and a mass was felt in the left hypochondrium. At operation, the mass was found to be infiltrating extensively into the surrounding structure, making removal impossible. Biopsy disclosed a renal cell carcinoma. He gradually deteriorated, and he died on July 26, 1976. The familial incidence of renal cell carcinoma may be fortuitous. (4 refs.)

77-0471 Wilms' Tumour and Neurofibromatosis. (Eng.) Walden, P. A. (Dept. Medical Oncology, Charing Cross Hosp., London W6 8RF, England) Johnson, A. G.; Bagshawe, K. d. *Br Med J* 1(6064): 813; 1977.

A case of a 3-yr-old black girl with Wilms' tumor and neurofibromatosis is presented. The patient was admitted on June 10, 1975, with a 6-mo history of a swelling in the abdomen. Physical examination demonstrated widespread cafe-au-lait spots over the chest, trunk, and arms. A large smooth mass was palpable in the left hypochondrium. The patient's father, a paternal aunt, and the paternal grandfather all had neurofibromatosis. An iv pyelogram showed distortion of the left kidney, with displacement by a soft mass extending across the midline. On June 20, a large nephroblastoma (15.5 × 10.5 cm), together with the left kidney and 6.5 cm of the ureter, were removed. To the naked eye, the tumor had not extended beyond the capsule of the kidney. Between July 1975 and July 1976 she received 11 courses of chemotherapy with actinomycin D and vincristine. She remains in remission with no evidence of recurrence. An underlying Wilms' tumor should not be excluded in any child with distinctive congenital anomalies. (5 refs.)

77-0472 Wilms's Tumour, Hypospadias, and Cryptorchidism in Twins. (Eng.) Bond, J. V. (Hosp. for Sick Children, Great Ormond St., London WC1N 1EH, England) *Arch Dis Child* 52(3): 243-245; 1977.

Twin boys, both of whom had hypospadias and bilateral cryptorchidism, each developed a left-sided Wilms' tumor. The first twin had an advanced multifocal tumor diagnosed at 15 mo of age, and he died with local recurrence and pulmonary metastases after undergoing a course of radiotherapy and nephrectomy. The diagnosis was made in the second twin 1 mo later; at nephrectomy, the tumor was found to be encapsulated, without metastases. This twin is disease-free after 12 yr. In both cases the tumor was composed mainly of rhabdomyosarcomatous tissue with areas of primitive mesenchyme, and there were attempts at early tubule formation. The tumors did not show the mirror-image pattern suggested for embryonal tumors in identical twins. There was no history of Wilms' tumor in the family, and a sister who was born 1 yr after the twins had no congenital abnormalities and is disease-free. Three cases of Wilms' tumor occurring in twins

have been reported in the literature. One involves the only reported pair of twins in which there was adequate evidence of monozygosity, but the second twin remains disease-free at the age of 5 yr. This case suggests that there is a variable degree of penetrance in the inheritance of Wilms' tumor. (14 refs.)

- 77-0473 Incidence of Renomedullary Interstitial Cell Tumors and Correlation with Hypertension.** (Eng.) Martin, M. R. (Dept. Pathology, Univ. Cape Town, South Africa) *S Afr Med J* 50(53): 2099-2100; 1976.

It has been suggested that renomedullary interstitial cell tumors occur in response to hypertension. In a study of 223 consecutive autopsies of subjects older than 17 yr, renomedullary interstitial cell tumors were found in 36 cases (25/130 males and 11/93 females). Only eight kidneys showed multiple lesions. The incidence of renomedullary interstitial cell tumors was not correlated with hypertension. The incidence of renomedullary interstitial cell tumors increases with age. The overall incidence of these tumors in this series, 16%, is lower than that of other reported series (30%-37%). (3 refs.)

- 77-0474 Resection of the Abdominal Wall in Metastasis from Cancer of the Bladder, Kidney or Colon.** (Eng.) Wahlgvist, L. (Urologiska Kliniken, Umea lasarett, S-901 85 Umea, Sweden) *Eur Urol* 3(1): 26-28; 1977.

Metastases in abdominal wounds were found to occur in about 1% of bladder cancer patients and less frequently in those with renal or colon cancer. Between 1963 and 1966, 409 new cases of bladder cancer were treated at a Swedish hospital. Of this group, metastases in the surgical wound were found in two women at autopsy. One had several metastases in the abdominal wall. Both had had anaplastic tumors that, at operation, were found to have grown through the muscular covering of the bladder. One had previously received radiation for cancer of the uterus, and the other had received preoperative irradiation of the bladder. Cancer in the abdominal wall was resected in four patients (3 men, 1 woman). The resection was extensive only in the woman, and she is alive without carcinoma 62 mo later. Her tumor was solid and spinocellular. Of the remaining three patients, one is alive after 12 mo, and two died after 24 and 36 mo. Out of 109 cases of renal carcinoma, abdominal wound metastasis was detected in only 1, a 60-yr-old man. Special problems that arise if metastases occur in a stoma for urine or feces are illustrated in the case report of a 77-yr-old man. Metastases in the vicinity of an ileostomy or colostomy may necessitate surgery. Radiation does not seem to provide any relief. (8 refs.)

- 77-0475 Tumors of the Bladder in Renal Transplant Patients: Report of a Case of Adenocarcinoma and Review of Known Cases.** (Eng.) Ito, T. Y. (Dept. Surgery-

Urology, Univ. California at Irvine, Irvine, CA) Martin, D. C. *J Urol* 11(1): 52-53; 1977.

Adenocarcinoma of the bladder occurred in a 35-yr-old man who had undergone renal transplantation 4 yr previously, in January 1971. The patient did well after the operation. Immunosuppression was maintained with 100 mg azathioprine daily and 45 mg prednisone on alternate days. In April 1975, the patient was treated for his first urinary tract infection since transplantation. The infection was readily cleared with antibiotics, but the patient was passing blood clots per urethra. Urinalysis revealed RBC too numerous to count. An excretory urogram revealed that the transplanted kidney in the left lower quadrant was unchanged from 1 yr previously. Cystoscopy revealed a 1-cm sessile lesion on the right posterior aspect of the bladder. The tumor was resected, and pathology revealed a moderately well-differentiated adenocarcinoma. The patient was discharged from the hospital but underwent a second resection 2 wk later to determine whether the margins of resection were clear. The pathology once again revealed adenocarcinoma, with no evidence of muscle invasion. On July 3, 1975, the patient underwent total cystectomy and ileal loop diversion from the transplant. Convalescence was uneventful, and the patient was discharged from the hospital 2 wk later. Pathologic examination of the bladder revealed no residual tumor. There are eight known cases of bladder tumors in renal transplant patients: four transitional cell carcinomas, two adenocarcinomas, one squamous cell carcinoma, and one nephrogenic adenoma. (6 refs.)

- 77-0476 Cholangiocarcinoma Associated with Biliary Cirrhosis due to Congenital Biliary Atresia.** (Eng.) Kulkarni, P. B. (Dept. Pediatrics, Children's Mercy Hosp., 24th and Gillham Road, Kansas City, MO 64108) *Am J Dis Child* 131(4): 442-444; 1977.

A case is reported of cholangiocarcinoma associated with biliary cirrhosis in an 11-yr-old girl. At 3 mo of age, a diagnosis of extrahepatic biliary atresia had been made. In March 1974, the patient was admitted because of persistent high temperature. Physical examination revealed an undernourished child with deformities of the lower extremities secondary to rickets and old healed fractures. Moderate icterus was present. The possibility of hepatic abscess was considered, and an exploratory laparotomy was performed. Repeated attempts to aspirate purulent material were unsuccessful. A biopsy specimen of multiple firm nodules (0.5-3.5 cm wide) in the liver showed liver carcinoma of the mixed hepatocellular and bile duct type. The patient died 8 days after the laparotomy. Microscopic examination of the liver demonstrated two distinct pathologic processes: (1) increased fibrous connective tissue in the portal triads with extension into the interlobular septa, and (2) diffuse infiltrative nodules of malignant neoplastic tissue, some representing bile duct components and others hepatocellular components. There may be a relation between the pathogenesis of biliary cirrhosis and liver carcinoma in children. (30 refs.)

7-0477 **Risk Indicators of De Novo Malignancy in Renal Transplant Recipients.** (Eng.) Sloan, G. M. (Dept. Surgery, Harvard Medical Sch., Boston, MA) Cole, J.; Wilson, R. E. *Transplant Proc* 9(1): 1129-1132; 1977.

The risk indicators of de novo malignancy in renal transplant recipients were investigated. De novo malignancy was diagnosed subsequent to renal transplantation in 23 patients. These patients were compared with 532 nonidentical twin renal transplant recipients. In addition, 46 matched controls (2 for each case) without malignancy were selected for further comparison. The mean age at transplantation for the cancer patients (44 yr) was 10 yr greater than the 532 other recipients (34 yr). Seventeen of the 23 cancer patients were men, compared with 328/532 of the other group. Thirteen of the 23 cancer patients had received cadaver kidneys, compared with 247 of the others. Five years after transplantation, 96% of the living cancer patients and 54% of the living controls had functioning kidneys. Throughout the 9-yr observation period, kidney survival was significantly higher for the cancer cases than for the controls. At the time of diagnosis of malignancy, 21/23 cancer cases had functioning kidneys. At the same time interval after transplantation, 27/46 controls had functioning kidneys. There is a remarkably good kidney survival in renal transplant recipients who have developed cancer. (12 refs.)

77-0478 **Occurrence of an Adenocarcinoma at the Cholechoenteric Anastomosis 14 Years After Pancreatoduodenectomy for Benign Disease.** (Eng.) Shields, H. M. (Gastrointestinal Section, 111H3, Univ. Pennsylvania Medical Service, Veterans Admin. Hosp., Philadelphia, PA 19104) *Gastroenterology* 72(2): 322-324; 1977.

The occurrence of an adenocarcinoma in a 49-yr-old black laborer is reported. Fourteen yr previously, the patient underwent a pancreatoduodenectomy for chronic pancreatitis. In February 1975, he presented with right upper quadrant pain and jaundice. A laparotomy was performed, but dense fibrotic tissue obscured all landmarks. A cholechoenteric anastomosis was obstructed by firm fibrous tissue containing small white lumps. Frozen sections revealed adenocarcinoma surrounded by dense fibrous tissue. The exact origin of the tumor, from the pancreas or biliary tract, could not be ascertained. Postoperatively, the right upper quadrant pain decreased, and the patient's appetite increased. The patient was placed on 5-fluorouracil (1,000 mg/wk iv), and he remained well for 3 mo after surgery. This case emphasizes the difficulty in arriving at a diagnosis in a patient with jaundice after a pancreatoduodenal section. The significance of the diagnosis lies in the known occurrence of benign strictures at the cholechojejunostomy site following a pancreatoduodenectomy. (12 refs.)

77-0479 **Metastasizing Islet Cell Carcinoma of the Pancreas in a 10-Year-Old Girl.** (Ger.) Nizze, H. (Institut für Allgemeine und Spezielle Pathologie, Wilhelm-

Pieck-Universität Rostock, DDR-25 Rostock 1, Strempeistrasse 14, E. Germany) *Zentralbl Allg Pathol* 120(6): 467-472; 1976.

The case history of a 10-yr-old girl with islet cell carcinoma of the pancreas with liver and peritoneal metastases is presented. The carcinoma was found at autopsy. Ultrastructurally, the cells showed typical secretion granules resembling prevailing A₁ (D) cell granules in pancreatic islets. Silver impregnation for demonstration of A₁ islet cells was moderately positive in the tumor cells. (26 refs.)

77-0480 **Secretion by Glucagonomas of a Possible Glucagon Precursor.** (Eng.) Weir, G. C. (Dept. Medicine, Massachusetts General Hosp., Boston, MA 02114) Horton, E. S.; Aoki, T. T.; Slovick, D.; Jaspán, J.; Rubenstein, A. H. *J Clin Invest* 59(2): 325-330; 1977.

The secretion by glucagonomas of a possible glucagon precursor was evaluated by chromatographing fasting plasma samples from five patients with these tumors on Bio-Gel P30 columns. There was a large amount of immunoreactive material in peak B, the 9,000-dalton region. The tumors were responsive to stimulation or suppression, as indicated by increases in total glucagon immunoreactivity during arginine infusion and 30 min after po glucose and the decreases after iv glucose. When the various patterns were analyzed, most of the change in total immunoreactivity could be accounted for by peak C, a 3,500-dalton glucagon. Before surgical removal, samples were obtained from veins draining the tumors of two patients. When compared with a peripheral venous sample in one patient and an arterial sample in the other, a significant increment of total glucagon immunoreactivity was observed in the venous effluent. Most of the increase was accounted for by peak C material. Furthermore, there was a clear increment in peak B. The two glucagonomas secreted primarily 3,500-dalton glucagon and relatively smaller amounts of the 9,000-dalton moiety. Plasma samples from two patients were chromatographed, and fractions of peak B and C were pooled separately. When different volumes from each pool were assayed, parallel displacement curves were noted, indicating the similar immunologic reactivity of these components with antiserum. With conversion to a neoplastic state, the alpha cells of glucagonomas may secrete an increased amount of a larger, 9,000-dalton glucagon species that may be a prohormone. (26 refs.)

77-0481 **Acinar Cell Neoplasms of the Exocrine Pancreas.** (Eng.) Webb, J. N. (Dept. Pathology, Western General Hosp., Edinburgh, Scotland) *J Clin Pathol* 30(2): 103-112; 1977.

Electron microscopy was used to investigate 12 patients with acinar cell neoplasms of the pancreas. The patients consisted of six women and six men, ages 25-85 yr. Most of the neoplasms were ductal adenocarcinomas, often with an abundant

stroma; mucin secretion was a common feature. Two tumors were intracystic papillary carcinomas, and six were frankly anaplastic. There were 11 acinar cell carcinoma, 7 pure and 4 mixed ductal and acinar types, plus 1 adenoma. The primary site was the head of the pancreas in six patients, the body in three, and the tail in two. The distinctive histologic features of these neoplasms and the means of differentiating them from anaplastic carcinomas and various other carcinomas are discussed. Pancreatic cancers have a poor prognosis. Future epidemiologic studies are needed to determine whether external carcinogens are implicated in their development. Carcinogenic factors that have been proposed are smoking, a high fat diet, and nitrosamines. (22 refs.)

- 77-0482 Acinar Cell Carcinomas of the Pancreas in a 9-Year-Old Child: Case Report with Electron Microscopic Observations.** (Eng.) Osborne, B. M. (Dept. Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Texas Medical Center, Houston, TX 77030) Culbert, S. J.; Cangir, A.; Mackay, B. *South Med J* 70(3): 370-372; 1977.

A case of acinar cell carcinoma of the pancreas in a 9-yr-old boy is presented in which the diagnosis was established by electron microscopy. In light microscopic sections of biopsy material, the neoplasm was seen to be composed of sheets of compactly arranged polyhedral cells with round central nuclei and scanty cytoplasm. There was no evidence of acinar formation. The neoplasm was thought to be a small cell carcinoma of undetermined origin. Electron microscopy confirmed the compact grouping of the tumor cells and the absence of acini. The most significant feature was the presence within the cytoplasm of large secretory granules, the majority of which were 1 micron in diameter, each with a closely limiting unit membrane. Treatment was by combination chemotherapy (actinomycin D, 9 µg/kg/day; 5-fluorouracil, 8 mg/kg/day; and cyclophosphamide, 7 mg/kg/day), and the survival time was 2 yr. At autopsy, a tumor having light and electron microscopic features identical to those seen in the biopsy material was found within the pancreas, invading the duodenal wall, compressing the common bile duct, and infiltrating the hilar connective tissue of the liver. Death followed extensive bleeding into the intestinal lumen from the ulcerated region of the duodenum. Without the aid of electron microscopy, the diagnosis would probably have remained carcinoma of undetermined type. (10 refs.)

- 77-0483 Oncolytic Lesions of the Caruncle and Other Ocular Adnexa.** (Eng.) Biggs, S. L. (Dept. Ophthalmic Pathology, Armed Forces Inst. Pathology, Washington, DC 20306) *Arch Ophthalmol* 95(3): 474-478; 1977.

In a clinicopathologic study, 18 rare cases of oncocytic lesions of the ocular adnexa were analyzed. There seemed to be a predilection for these lesions in elderly patients (median age

73) and in women (11/18 patients). This supports the view that transformation to oncocytes may be related to aging. Diagnoses ranged from oncocytomas to oncocytic hyperplasia and oncocytic carcinoma. Ten of the lesions, all of which were oncocytomas, arose in the caruncle, 2 in the bulbar conjunctiva, 2 in the fornical conjunctiva, and 1 in the mucocutaneous junction of the eyelid. Two tumors involved the lacrimal sac and one the lacrimal gland. Follow-up information on a single case of oncocytic carcinoma of the lacrimal gland could not be obtained. Perhaps the oncocytic lesions developed from oncocytic metaplasia of ducts and acinar cells of the lacrimal or salivary glands located in the ocular adnexa. One oncocytoma associated with squamous cell papilloma may have originated from oncocytic transformation of conjunctival epithelium. (21 refs.)

- 77-0484 Ocular Malignant Diseases, Embryonal Sarcoma.** (Eng.) Lederman, M. (Royal Marsden Hosp., Fulham Road, London SW3 6JJ, England) Wybar, K. *Proc Royal Soc Med* 69(12): 895-903; 1976.

A series of 29 children (15 boys and 14 girls aged up to 18 yr) with embryonal sarcoma affecting the region of the eye is discussed. In the majority of these patients, the presenting features of the tumor were usually trivial, making diagnosis difficult. Most common was a swelling of the upper eyelid (11), followed by lower eyelid (3), both lids (2), tissues of the medial canthus (3), lateral canthus (1), superior fornix (1); and inferior fornix (2) and a proptosis (4). Usually there was a fairly sudden change in the nature of the presenting symptoms, and in all but 6/29, this took the form of a marked proptosis or an obvious increase in the proptosis that was the presenting symptom. Treatment consisted primarily of irradiation, usually external beam therapy in doses of 5,000-7,000 rads over 6-8 wk for 24 patients; in 5 it followed other forms of surgical treatment. Exenteration was performed as a primary procedure in 3 cases and as a secondary procedure in 11 cases. Perfusion was done in 8 patients who failed to respond to the other therapies. Seventeen patients failed to survive. For embryonal sarcoma, the policy of immediate biopsy of any suspicious lesion is recommended, with immediate irradiation in sufficient doses to the entire involved area, exenteration of the orbital contents in the event of recurrence, and perfusion when there is recurrence after exenteration. (4 refs.)

- 77-0485 Squamous Cell Carcinoma Developing in an Orbital Cyst.** (Eng.) Wright, J. (Moorfields Eye Hosp., London, England) *Arch Ophthalmol* 95(4): 635-637; 1977.

A case of squamous cell carcinoma in the wall of an orbital cyst in a 53-yr-old man is presented. The patient was admitted with a 2-mo history of distorted vision, with pain and swelling of the upper part of the right eyelid. The right eye was proptosed and displaced downward and inward by a large tender mass in the upper and outer orbit. Roentgeno-

rams of the skull demonstrated an area of pressure erosion of the bone overlying the right lacrimal gland. A cyst that adhered to the globe and the optic nerve and extended back to the superior orbital fissure was excised. It measured $34 \times 20 \times 20$ mm. Stained sections showed no evidence of a normal epithelial lining nor any dermal elements such as hair follicles or sebaceous glands. The tumor was a well-differentiated, keratinizing squamous carcinoma. Eleven months later, the tumor recurred. The patient died shortly afterward. The case seems to be unique, since the tumor probably had its origin in a congenital epidermoid cyst. (2 refs.)

77-0486 **The Occurrence of "Fleurettes" in Retinoblastoma.** (Hun.) Radnot, M. (SOTE 1. sz. Szemeseti Klinika, Budapest, Hungary) *Magy Onkol* 20(4): 250-53; 1976.

The occurrence of "fleurettes" in 3 of 29 retinoblastoma patients is discussed. These cells resemble the rudimentary photoreceptor processes in the periphery of the retina. The occurrence of these "fleurettes", synaptic lamellae and vesicula, and proof of the neural origin of retinoblastomas, are discussed. (10 refs.)

77-0487 **Sporadic Bilateral Retinoblastoma and 13q-Chromosomal Deletion.** (Eng.) Francke, U. (Dept. Pediatrics, Univ. California, San Diego, La Jolla, CA 92093) *Kung, F. Med Pediatr Oncol* 2(4): 379-385; 1976.

The case of a 6-yr-old girl with bilateral sporadic retinoblastoma is presented. At 6 mo of age, enlargement of the right eye was observed. When retinoblastoma was diagnosed at 8 mo, the right eye was enucleated. The diagnosis was confirmed histologically. Small patches of retinoblastoma in the left eye regressed after radiotherapy. The child was followed closely in the pediatric oncology and ophthalmology clinics, and no evidence for tumor recurrence was found over a 5-yr period. The mitotic rate in phytohemagglutinin-stimulated lymphocyte cultures was significantly low on two separate occasions. G-bands were produced by Giemsa-trypsin staining. All of 20 metaphases analyzed contained 46 chromosomes, including a chromosome 13 with a small interstitial deletion from the long arm. The most proximal dark band 13q13 was missing, presumably due to breaks in bands 13q13 and 13q14. There was no evidence for translocation of the missing material onto another chromosome. A skin biopsy failed to grow out fibroblasts. Both parents had normal G-banded karyotypes. The cytogenetic findings in the patient were compared with three reported cases studied by banding techniques. In one patient, the deletion involved a similar region, while in two, the deleted segment was more proximal in the long arm. The faintly staining band 13q14 appeared to be the only overlapping segment in these different deletions. This site is proposed as the precise location of a gene involved in retinal development. (26 refs.)

77-0488 **Bilateral Choroidal Melanomas. Case Report and Incidence.** (Eng.) Shammas, H. F. (Dept. Ophthalmology, Univ. Iowa Hosp., Iowa City, IA 52242) Watzke, R. C. *Arch Ophthalmol* 95(4): 617-623; 1977.

A case of bilateral choroidal melanoma in a 55-yr-old woman is presented. The patient was examined in September 1970 because of blurred vision in the right eye. A mass was noted in the posterior pole of the eye, and the eye was subsequently enucleated. Microscopically, the tumor was amelanotic and of the epithelioid cell type. The patient was not seen again until December 1974. She had noted some visual field loss and dimness of vision. There was an obvious elevated mass in the superotemporal quadrant. Excision of the tumor by local wall resection was not considered feasible because of surrounding serous detachment. It was decided, therefore, to use radiation therapy. The patient was followed up until October 1975, when enucleation was advised. Examination of the pathological specimen disclosed a dark gray mass with patchy black pigmentation over its surface. Macroscopically, a mushroom-shaped choroidal tumor was present just behind the equator. Microscopically, the tumor was lightly pigmented and of the spindle cell B type. Bilateral choroidal melanoma is expected to occur once every 18 yr in the US. (32 refs.)

77-0489 **Do Polyunsaturated Fats Predispose to Malignant Melanoma? [Letter to Editor].** (Eng.) Mackie, B. S. (187 Macquarie St., Sydney, New South Wales 2000) *Med J Aust* 2(21): 806; 1976.

The possible association of polyunsaturated fats with malignant melanoma is assessed. In January, 1972, a patient was seen who had been previously treated over a period of years for simple keratoses, and developed three separate squamous cell carcinomas of the skin within 4 mo. The only significant fact was that he had changed to a polyunsaturated fat diet 6 mo before the first squamous cell carcinoma appeared. It was suggested that he go back to his previous diet, and he has not had a squamous cell carcinoma since. In the next 2 yr, two more patients were seen with the same story and the same result. In the summer of 1973-1974, five patients with malignant melanoma were observed. These patients required extensive surgery, and they had to cope with the threat of metastases. A dietitian interviewed four of the five patients, and she determined that all of them had substantially reduced their intake of saturated fat and replaced it with polyunsaturates. The fifth patient was under the supervision of a cardiologist, who indicated that the diet was fully polyunsaturated. Patients with primary lesions on sites of most frequent trauma might show less evidence of a dietary factor than other melanoma patients. The sites of most frequent trauma are the head and neck, the hands and feet, the groins, axillae, genitals and buttocks. Lesions with the highest malignant activity would be likely to show the strongest causative influences and perhaps a combination of factors. A series of patients with metastases may well demonstrate more evidence of a dietary factor than those with secondary spread. A significant difference between fat analyses for the cases of traumatic lesions

and those metastases would be evidence that dietary lipids are involved. (3 refs.)

- 77-0490 A Case Report Including EM and DNA Repair Investigations in a Dermatoses Associated with Multiple Skin Cancers: Epidermodysplasia Verruciformis.** (Eng.) Hammar, H. (Dept. Dermatology, Karolinska Hosp., Stockholm, Sweden) Hammar, L.; Lambert, B.; Ringborg, U. *Acta Med Scand* 200(6): 441-446; 1976.

A case of epidermodysplasia verruciformis (EV) in a 51-yr-old man is presented. On physical examination, the patient displayed many keratotic and ulcerated lesions on the face and earlobes. A cicatricial atrophic area around the left eye was observed, and an induration was seen in a transplant on the right cheek. On the buccal aspect of this area, there was a hard, ulcerated, papillomatous lesion. The extremities and the trunk were covered with slightly elevated scaling papules and several keratotic lesions, indicating a possible Bowenoid transformation. The lesions suggestive of a plane wart demonstrated a patchy or continuous abundance of clear cells near the corneal layer and extending in some areas down to the suprabasal layer. The subcorneal clear cells contained many abnormal keratohyalin granules in the cytoplasm. Tonofilaments were sparse, and many enlarged mitochondria exhibited cristolysis. Electron microscope micrographs displayed cells with normal desmosomes, sparse in tonofilaments, rich in cytoplasmic organelles with cristolysis in mitochondria and with a nucleus containing two or more nucleoli. Hydroxyurea depressed the replicative DNA synthesis to approx the same level in WBC from the patient and nine controls. The patient showed a 40% reduction of UV-induced DNA repair synthesis compared with av control values. The results suggest that a decrease in UV-induced DNA repair synthesis in combination with a possibly oncogenic viral infection may increase the disposition for somatic mutations and malignant transformation in EV patients. (16 refs.)

- 77-0491 Basal Cell Carcinoma in Tattoos: Report of Two Cases.** (Eng.) Bashir, A. H. (Dept. Plastic Reconstructive Surgery, Coll. Medicine, Univ. Basrah, Basrah, Iraq) *Br J Plast Surg* 29(4): 288-290; 1976.

Two cases of basal cell carcinoma in tattoos are presented (tattooing is a therapeutic practice in Iraq, where the two patients live). A 60-yr-old housewife had been tattooed on her right temple with carbon pigment 20 yr earlier in a fruitless attempt to relieve her headaches, which were in fact due to hypertension. Three yr ago, she observed a small nodule in the center of the tattooed skin at the outer end of the right eyebrow, which was also tattooed for cosmetic reasons. The lesion had grown into an ulcer 7-8 mm in diameter with the typical appearance of a basal cell carcinoma. The diagnosis was confirmed histologically after excision. A 52-yr-old farmer had been tattooed 15 yr before on his right temple with carbon pigment for intermittent headache, which, he

claimed, had been relieved ever since. The association of relief of pain with acupuncture is known and may explain the occasional relief of headache after tattooing. Four yr ago, a skin lesion appeared in the tattooed skin and later ulcerated and was excised, and histology confirmed the diagnosis of basal cell carcinoma. Approx 90% of the patients have tattoos. During the past 3 yr, 750 patients have been operated upon as inpatients and about 2,000 as outpatients. Since the cases reported are the only two instances where a basal cell carcinoma arose in an area previously tattooed, it is concluded that the occurrence is almost certainly a coincidence. (4 refs.)

- 77-0492 Cancer of the Skin and the Precancerous Stages in the Epidermal-Dermal Interface.** (Eng.) Oberste-Lehn, H. In: *Cancer of the Skin. Biology-Diagnosis-Management.* Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 189-223; 1976.

Precancerous, pseudocancerous, and neoplastic alterations of the epithelium are discussed. A method for the preparation of plastic figures of the epidermal-dermal interface is described. The surface of the epithelium obtained shows the epithelial structures at their interface with the corium. Characteristic features at the epidermal-dermal interface are described for a number of dermatoses, including eczema, neurodermatitis, scar tissue, atrophy, discoid and chronic lupus erythematosus, verrucous lichen planus, drug eruption, bullous pemphigoid, senile keratosis, and acanthosis. The most diverse lesions exhibit repeated, identical alterations; these are parallel or radial rete ridges running toward the focus of the lesion, which turns into a scar or atrophy in its final stage. The rete ridges found around the hair follicles and excretory sweat glands are of special importance in various dermatoses. An irreversible skin alteration results when the ridges and the sweat gland ducts, alone or together with the appendages, are destroyed. These specific epithelial ridges around the appendages generally do not participate in the formative changes undergone by the other ridges during the pathologic process. When they are affected by disease, the result is also a scarred or atrophic epithelium. Growth or degenerative impulses apparently start from the epithelium of the appendages or the specific rete ridges around them. (48 refs.)

- 770493 Double Primary Carcinoma of the Lips.** (Eng.) Pisanty, S. (Dept. Oral Diagnosis, Oral Medicine Roentgenology, Sch. Dental Medicine, Jerusalem, Israel) *Oral Surg* 43(4): 524-527; 1977.

A case of double squamous-cell carcinoma of the lips occurred in a 40-yr-old man, who was first seen in September 1974. The two ulcerative lesions had first been noted approx 1 yr previously. The man had smoked up to 20 cigarettes per day for approx 20 yr. One lesion was a 1.5-cm ulcerated and indurated exophytic mass in the middle of the lower lip and the other was a 1-cm ulcerated and indurated lesion in the middle

f the upper lip. The two were widely excised; upon microscopic examination of the tissue, they proved to be malignant. Healing was uneventful, and the prognosis was considered good. The patient stopped smoking, and he used UV protective cream on his lips. Repeated 3-mo observations for 2 yr were negative. When oral cancer develops, all mucous membrane surfaces must be considered highly susceptible to future malignant change. (11 refs.)

77-0494 **Nasal Hemangiopericytoma.** (Eng.) Brown, J. A. (PO Box 1226, Anderson, SC 29621) *South Med J* 70(3): 359-360; 1977.

A case of nasal hemangiopericytoma with multiple myeloma presented. The patient was a 55-yr-old man with a gradual 5-yr increase in nasal obstruction. Routine laboratory tests, including sinus roentgenograms, were normal, but blood and bone marrow studies indicated multiple myeloma. Laminograms revealed a large dense mass filling the ethmoids and nasal vestibule. Using an extended lateral rhinotomy approach, a large fleshy tumor extending from the right middle meatus into the anterior and posterior ethmoids and into the sphenoid sinus was removed. The patient received radiation therapy and is undergoing chemotherapy with melphalan and prednisone for the multiple myeloma. Two yr after the operation, there is no evidence of local recurrence or metastasis, and the myeloma appears to be under control. Hemangiopericytoma is usually described as a mass that manifests no pain or sensation, causes obstruction, and is benign-looking. It may be an extremely aggressive tumor locally and may manifest a high recurrence rate. Metastatic rates vary from 15%-45% and have included osseous, hepatic, and pulmonary metastases. Wide local excision is the treatment of choice. Few deaths occur during the first 5 yr, but the mortality is high with a long follow-up. The treatment of this disease, therefore, requires a lifetime evaluation with aggressive initial therapy. (5 refs.)

77-0495 **Traumatic Neuroma of the Nose.** (Eng.) Burtner, D. D. (1261 Furnace Brook Parkway, Quincy, MA 02169) Goodman, M. *Arch Otolaryngol* 103(2): 108-109; 1977.

A case of a traumatic neuroma of the nose in a 16-yr-old boy is reported. The patient was referred for removal of a cyst on the left side of the columella. He had injured his left upper lip immediately below the columella at age 4. The laceration had been sutured closed, and the patient had noted no further difficulty with this area until 5 yr ago, when he sustained a blunt injury to the same area and subsequently observed the development of a firm, painless, rounded 1.0- x 1.5-cm mass enveloping the left mesial crus. On gross examination, the specimen seemed to be oval and firm, and, on section, whitish and avascular. Microscopic examination demonstrated an outer connective tissue intermixed with a central area of axons with intact nerve trunks. Two wk after surgery, the columella

had healed satisfactorily, and both sides of the nose were symmetrical. The patient returned 10 wk later, however, with a 1.0- x 1.5-cm, firm, reddish mass in the same location. He revealed that he had been hit by a football about 4 wk previously. The tissue appeared to be different from the previously excised traumatic neuroma. Microscopic histologic examination demonstrated fibrosis and chronic inflammation with focal foreign-body reaction, without evidence of a neuroma. Ten days after surgery, 4 ml of a 3.3-mg/ml soln of triamcinolone acetonide was injected. One month later, this was repeated with a total dose of 0.25 mg. The area healed satisfactorily. (6 refs.)

77-0496 **Carcinoma of the External Ear.** (Eng.) Pless, J. (Dept. Plastic Surgery, Finsen Inst., Copenhagen, Denmark) *Scand J Plast Reconstr Surg* 10(2): 147-151; 1976.

Between 1947 and 1967, 246 patients were surgically treated for 259 carcinomas of the external ear. There were 36 women and 210 men. Left- and right-sided carcinomas were equally distributed. Half of the carcinomas were sited on the helix and lobe, one-fourth were medial, and one-fourth were lateral. There were 177 squamous cell carcinomas and 79 basal cell carcinomas. The 3-yr rates without recurrence for basal cell carcinoma and squamous cell carcinoma were 87% and 85%, respectively; the 5-yr rates without recurrence were 82% and 83.5%, respectively. Basal cell carcinomas did not metastasize as did 3% of the squamous cell carcinoma recurrences. In the basal cell carcinoma group, 65% were alive 3.5 yr later, while 59% were alive after 5 yr. The same survival rates for squamous cell carcinoma were 62% and 55%, respectively. There was a greater tendency for recurrence in large tumors (> 40 mm); whereas, the seriousness of small basal cell carcinomas seemed to be underestimated, providing a tendency to limited excision. (17 refs.)

77-0497 **Central Leiomyoma of the Mandible. Report of a Case with Ultrastructural Confirmation.** (Eng.) Goldblatt, L. I. (Dept. Oral Pathology, Indiana Univ. Sch. Dentistry, 1121 W. Michigan St., Indianapolis, IN 46202) *Oral Surg* 43(4): 591-597; 1977.

A case of central leiomyoma of the mandible is presented in a 3 1/2-yr-old girl. The patient had a 2- x 2.5-cm radiolucency associated with the erupted mandibular left deciduous molars. At operation, a rough-textured, freely bleeding mass was enucleated, along with two involved deciduous molars. Histological examination revealed several fragments of soft tissue composed of interlacing fascicles of spindle cells in a partly amorphous and partly collagenous stroma. Two principal types of cells could be identified electron microscopically. The first type exhibited an elongated nucleus with gently rounded or blunted ends, a multiply indented or "wrinkled" nuclear membrane, and a prominent nucleolus. The second exhibited a round to ovoid nucleus, a relatively smooth membrane, a variably prominent nucleolus, and cytoplasm con-

taining abundant amounts of dilated rough endoplasmic reticulum. The diagnosis was central leiomyoma of bone. Clinical and radiographic examination of the patient 25 mo postoperatively revealed normal healing, bone regeneration, and normal development of permanent tooth buds. This is only the second report of a leiomyoma arising centrally within bone. (20 refs.)

77-0498 Evidence for an Association Between Uncommon Gm Phenotypes and Neuroblastoma. (Eng.)

Morell, A. (Inst. Clinical Experimental Cancer Res. Univ., 3004 Berne, Switzerland) Scherz, R.; Kaser, H.; Skvaril, F. *Lancet* (8001): 23-24; 1977.

Evidence for an association between neuroblastoma and uncommon Gm phenotypes is presented. Serum samples from 68 patients with clinically, biochemically, and histologically confirmed neuroblastoma, from 14 relatives of 1 patient (case A) and from 2,733 normal blood donors were studied. Patients were aged from 2 days to 13 yr 2 mo. In 42 of these children, tumor activity was present at the time of the investigation. In the other 26 patients, no signs of tumor activity could be detected. Remission after therapy in these 26 patients had lasted from 2 mo to 6 yr at the time of the study. Patients with active disease and patients in remission were combined for statistical analyses, since the distribution of Gm phenotypes did not differ between the two groups. The allotypes Gm(a), Gm(f), Gm(g), and Gm(b) were determined by a passive hemagglutination-inhibition assay. The combinations of these four Gm allotypes in individual sera were designated as their Gm phenotypes. In normal blood donors, the frequency of all three common and of both of the two uncommon Gm phenotypes resembled reported values. However, when the neuroblastoma group was compared with the normal blood donors, the increased frequency of uncommon Gm phenotypes in the neuroblastoma patients became evident. Frequencies of the uncommon phenotype Gm(a+ f+ g- b+) in the neuroblastoma group and in the blood donor population were significantly different. The combined frequency of both rare phenotypes was also significantly different in the two groups. Differences in the distributions of the three common Gm phenotypes between the two populations were not significant. Of the nine patients with uncommon phenotypes, six had active disease and the other three were in remission. In case A, the patient, her mother, and one of her sisters had an uncommon Gm haplotype on one chromosome, where the immunoglobulin (IgG)1 gene Gm(2a) was not associated with the IgG3 gene Gm(g) but with a rare IgG3 allele (zab⁶stb¹b³). This gave rise to the rare haplotype Gm(a+ g-) and thus to the rare phenotype Gm(a+ f+ g- b+). The study demonstrates that neuroblastoma is associated with the uncommon Gm phenotype Gm(a+ f+ g- b+) and possibly also with Gm(a+ f+ g+ b-). (9 refs.)

77-0499 Central Neuroblastoma. Electron Microscopic Observations and Catecholamine Determinations. (Eng.) Azzarelli, B. (Div. Neuropathology, Inst. Pa-

thology, Case Western Reserve Univ., Cleveland, OH 44106. Richards, D. E.; Anton, A. H.; Roessmann, U. *J Neuropathol Exper Neurol* 36(2): 384-397; 1977.

A case of cerebral neuroblastoma in an 18-mo-old boy is reported. The patient was admitted to the hospital in decerebrate coma. Cerebral angiography revealed an avascular left frontal mass with hydrocephalus. An air-Conray ventriculogram outlined a lobulated, left anterior, intraventricular mass blocking the foramen of Monro. The cerebrospinal fluid was bloody, and the pressure was increased. Thirty hr after admission, the patient underwent a left frontal craniotomy, with removal of the intraventricular tumor by suction. The tumor arose from the anterolateral wall of the left lateral ventricle and occluded the foramen of Monro, but it did not invade deeply into the brain. A focal seizure disorder and intermittent spiking fevers associated with hypothermia complicated the hospital course, and the patient died 6 mo after admission. The highly cellular tumor was composed of closely packed cells showing moderate variation in size and ill-defined, scanty cytoplasm. The most common cell had scant cytoplasm with relatively few cisterns of the granular endoplasmic reticulum, regular amounts of ribosomal rosettes, and a few mitochondria. Chemical determinations revealed increased catecholamine levels in the cerebrospinal fluid and urine. (42 refs.)

77-0500 Maturing Neuroblastoma and Ganglioneuroblastoma: A Study of Four Cases with Long Survival. (Eng.) McLaughlin, J. E. (Royal Free Hosp., Pond St., London NW3 2QG, England) *J Pathol* 121(1): 19-26; 1977.

A retrospective study of four children (8 mo-8 yr old) with tumors of the peripheral nervous system, originally diagnosed as neuroblastomas or ganglioneuroblastomas, is presented. All the patients have survived, one for 14 yr. Residual tumor was seen in only one patient; it shows evidence of histological differentiation. All patients underwent surgery; one received radiation and another, chemotherapy. The authors suggest that even small areas of maturation indicate a good prognosis. Maturing tumors may metastasize and invade, but the prognosis may still be good. (49 refs.)

77-0501 Diffuse Osteoblastic Metastases from an Intracranial Glioma. (Eng.) Schatzki, S. C. (Dept. Radiology, Mount Auburn Hosp., 330 Mount Auburn St., Cambridge, MA 02138) McIlmoyle, G.; Lewis, S. *Am J Roentgenol* 128(2): 321-323; 1976.

An unusual case of a metastatic glioma presenting with diffuse osteoblastic lesions is reported in a 56-yr-old man who had a right frontal glioma surgically removed in 1968 and then died almost 8 yr later of extracranial metastases. Films taken in 1975 after the original craniotomy showed diffuse sclerosis of the skeleton involving the thoracic and lumbar spine, pelvis, ribs, clavicles, and proximal femurs. The peri-

pheral bones were not examined. A "super bone scan" of the skeleton was obtained with 15 mCi ^{99m}Tc MDP. The changes suggested metastatic prostatic carcinoma or agnogenic myeloid metaplasia. A survey of primary brain tumor patients has suggested that tumor cells may enter blood vessels during surgery and, therefore, have the potential for widespread metastases. (13 refs.)

- 77-0502 **Fine Structure of Myomedulloblastoma.** (Eng.) Stahlberger, R. (Dept. Neuropathology, Inst. Pathology, Univ. Zurich, Schmelzbergstr. 12, CH-8091, Zurich, Switzerland) *Acta Neuropathol (Berl)* 37(1): 43-48; 1977.

An electron microscopic study was made of a medulloblastoma containing smaller components of myoblastoma that was removed from a 2.5-yr-old boy. The data support the concept that medulloblastoma and myoblastoma components of the tumor proliferate side by side and originate from two different cell lines. The fine structure of the undifferentiated cells in the myoblastoma component was similar to that of developing skeletal muscle in the chick and that of satellite cells in mouse skeletal muscle. These undifferentiated cells were joined to the well-differentiated muscle cells by a common basement membrane and by cell junctions resembling desmosomes. None of the cells of the medulloblastoma portion of the tumor had a basement membrane. Furthermore, the envelopment of a neuroectodermal and of a mesodermal cell by a common basement membrane has never been observed. (18 refs.)

- 77-0503 **Malignant Transformation of Ameloblastic Fibro-odontoma to Ameloblastic Fibrosarcoma.** (Eng.) Howell, R. M. (Dept. Oral Pathology, Univ. North Carolina Sch. Dentistry, Chapel Hill, NC 27514) *Oral Surg Oral Med Oral Pathol* 43(3): 391-401; 1977.

The case histories are presented of two patients in whom benign ameloblastic fibro-odontoma transformed into malignant ameloblastic fibrosarcoma. The odontogenic neoplastic issues were examined histologically at various stages of the disease in both cases: the connective tissue stroma progressively lost its benign appearance and became malignant. As this sarcomatous pattern developed, the amount of odontogenic epithelium was diminished. A brief review of the literature on ameloblastic fibrosarcoma is presented. (35 refs.)

- 77-0504 **Iatrogenic Intraspinal Epidermoid Tumors.** (Eng.) Batnitzky, S. (Dept. Radiology, Indiana Univ. Sch. Medicine, 1100 West Michigan St., Indianapolis, IN 46202) Keucher, T. R.; Mealey, J.; Campbell, R. L. *JAMA* 237(2): 148-150; 1977.

Three cases of iatrogenic intradural epidermoid tumors in children, each of whom had one or more lumbar punctures

3.5-6 yr before the onset of their symptoms, are described. A 7-yr-old girl had a 2-yr history of progressive back pain, which radiated down both legs. Findings from a physical examination showed increased lordosis of the lumbar area and bilateral contracted hamstring muscles, which were moderately weak. A cystometrogram demonstrated an early neurogenic bladder of the flaccid type. Myelography showed an intradural mass extending from the mid-portion of L-3 to L-5. At operation, an obvious intradural epidermoid tumor was found situated mainly posteriorly and central in location between L-3 and L-5. The tumor distended the cauda equina rootlets. The tumor was adherent to some of the nerve roots, and areas of dense arachnoiditis were identified posteriorly. The tumor was excised. Postoperatively, the patient was relieved of her pain and made an uneventful recovery. A 5-yr-old boy was admitted to the hospital complaining of left hip and leg pain for a period of 6 wk. An intradural pearly epidermoid tumor measuring 2 cm in diameter at the level of L-4 to L-5 was found at operation and excised. The tumor was adherent to the left L-5 nerve root. The patient's postoperative course was one of progressive improvement. He resumed a good ambulatory status and was relieved of his pain. A 9.5-yr-old boy had a 6-mo history of progressive pain in his left midcalf region. At operation, an obvious intradural epidermoid extending from the inferior edge of the body of L-3 to L-5 was found and excised. The tumor was adherent to the dura at the posterolateral aspect of the dural sac. In this region of the dura, there appeared to be sites where lumbar punctures had been done. Postoperatively, the patient's pain subsided, and he made an uneventful recovery. A myelography should be considered for every patient who has had previous lumbar punctures and who has pain in the back or lower extremities. (8 refs.)

- 77-0505 **A Chordoma of Sacrococcygeal Region as a Cause of Nephrotic Syndrome.** (Ger.) Papadimitriou, K. (Inst. Pathology, Goudi Univ., Athens (617), Greece) Nakopoulou, L.; Billalis, D.; Papacharalampous, X. N. *Zentralbl Allg Pathol* 120(6): 500-504; 1976.

The case history of a 27-yr-old man with a chordoma of the sacrococcygeal region connected with a nephrotic syndrome is presented. Biopsy of the kidney revealed a diffuse membranous glomerulonephritis. Immunofluorescence revealed deposits of IgG on the basal membrane of the glomeruli. Autoantibodies against chordoma cells were found in the patient's serum. IgG globulins were also detected. This is believed to be the first case of chordoma connected with the nephrotic syndrome. (10 refs.)

- 77-0506 **Coincidence of Intracranial and Spinal Meningioma in a Patient with Recklinghausen's Disease.** (Ger.) Waldbaur, H. (Neurochirurgische Universitätsklinik, Krankenhausstrasse 12, D-8520 Erlangen, W. Germany) Schmidt, H. *Zentralbl Neurochir* 37(2): 131-135; 1976.

A large meningioma of the right wing of the sphenoid bone and a spinal meningioma in the region of the first thoracic vertebra were diagnosed and extirpated at a 1-mo interval in a 22-yr-old man suffering from Recklinghausen's disease, cafe-au-lait spots, and skin tumors. A bilateral acoustic neurinoma was found a few months later. The patient's mother had had multiple intracranial meningiomas and a bilateral acoustic neurinoma. Most likely, she also had Recklinghausen's disease. The findings indicate that multiple meningiomas in meningioma patients, especially those with Recklinghausen's disease, should be considered upon suspect findings. (13 refs.)

- 77-0507 **Studies of a Transplantable Rat Pheochromocytoma.** (Eng.) Murphy, G. P. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263) Williams, P. D.; Sufrin, G. S.; Mirand, E. A. *Oncology* 33(3): 114-115; 1976.

Studies of a transplantable rat pheochromocytoma are presented. A tumor mass of approx 1 x 1 x 3 mm was transplanted by trocar sc in the interscapular region. Untreated tumor-bearing New England Deaconess Hospital rats survived 49 days from tumor implantation until death in 59 cases. Control (non-tumor-bearing) animals all lived longer than 60 days and could readily be maintained for over 6-12 mo. The av gross tumor size at death was 2.3 x 1.1 x 0.8 cm. At the time of death, tumor-bearing rats had lost 27% of their initial body wt, compared to controls. Fresh, wet gross tumor wt at the time of death was 1.1 g. Microscopic and gross assessment of the 59 rats confirmed one instance of pulmonary metastases. Focal necrotic and secondary changes in the local tumor were grossly evident at the site of tumor implantation. The primary tumor exhibited relatively large cells, some pleomorphism, and invasion of the adjacent musculature. Electron microscopic studies confirmed tumor-related intracytoplasmic granules not found in healthy rat adrenal medullary tissue. Selected sacrificed tumor-bearing and healthy rats did not exhibit anemia or polycythemia. Tumor-bearing animals did not have significant erythropoietin elevations. Suitably prepared extracts of the primary tumor did not exhibit increased erythropoietin activity. In contrast, in tumor-bearing rats, erythropoietin activity in kidney extracts was significantly reduced. Random histological inspection of the kidneys failed to reveal the presence of any metastatic foci. The results indicate that the pheochromocytoma tumor can be successfully transplanted into rats. (5 refs.)

- 77-0508 **Morphology and the Natural History of Cribriform Adenocarcinoma (Adenoid Cystic Carcinoma).** (Eng.) Osborn, D. A. (Inst. Laryngology and Otolaryngology, Univ. London, England) *J Clin Pathol* 30(3): 195-205; 1977.

Forty-three cases of cribriform adenocarcinoma (adenoid cystic carcinoma) of mixed glandular origin identified between 1948-1973 were examined by light microscopy and his-

tological procedures and some by electron microscopy. Thirty-four tumors were cribriform adenocarcinomas of the mucosal glands, 5 tumors of similar structure were seen in neoplasms of major salivary glands, and 4 were found in a group of tumors of the external auditory meatus designated ceruminomas. Structural studies indicated the classical cribriform pattern, which indicates the capacity of this neoplasm to behave as both an epithelial and a connective tissue type tumor. All cases were treated by varying combinations of surgery and irradiation. The 14 surviving cases were comprised of 10 mucosal gland, 2 parotid, and 2 aural tumors. Six cases died from unrelated causes and six were lost to follow-up. Recurrence took place in 16 mucosal, 2 parotid, and 2 aural tumors. In terms of survival, therefore, cribriform adenocarcinoma does not appear to be as malignant as other forms of carcinoma arising in similar anatomical locations. The 5-yr crude survival rate (56%) compares favorably with that of other carcinomas of the palate and paranasal sinuses, although there is clearly a high morbidity. (50 refs.)

- 77-0509 **Thyroid Cancer After Irradiation.** (Eng.) Chang-Chien, Y. (Dept. Surgery, Natl. Taiwan Univ. Hosp., Taipei, Taiwan, Republic of China) Liaw, K. Y.; Wang, D. J.; Chen, F. W. *Int Surg* 62(2): 112-114; 1977.

The cases of nine thyroid cancer patients who had previously been exposed to radiation in the thyroid region (4 for breast cancer, 1 for a skin lesion, and 4 for hyperthyroidism) are reported. A 10-yr-old boy received 600 rads of deep x-ray treatment on the neck for a skin lesion. Thirteen years later he underwent thyroidectomy, and he has done well for 5 yr since then. Four women (aged 33-59 yr at the time of irradiation) received postmastectomy ⁶⁰Co or deep x-ray irradiation in a total dose of 4,000-5,000 rads to the chest and supraclavicular region for breast cancer 9-13 yr before thyroidectomy. One patient died of a cerebral vascular accident 18 mo after surgery, but the other three did well. Two women (aged 40 and 44 yr at the time of irradiation) received ¹³¹I radiation for hyperthyroidism. The onset of thyroid cancer (1.4 and 10 yr later, respectively) was not clear in either case. Both patients underwent a near-total lobectomy of the affected side and isthmusectomy and subtotal lobectomy of the opposite side. They have done well for 10 and 5 yr, respectively, since surgery. Two men (aged 19 and 29 yr at the time of irradiation) also received ¹³¹I radiation for hyperthyroidism. Thyroidectomy was performed 7 and 12 yr later, respectively. The former has done well for 4 mo since surgery, but the latter died 2 mo later. The potential carcinogenic effect of radiation cannot be ruled out. (16 refs.)

- 77-0510 **The Ultrastructure of Human Pituitary Adenomas.** (Ger.) Zotter, S. (Pathologisches Institut, Medizinische Akademie "Carl Gustav Carus", DDR-8019 Dresden, Fetscherstrasse 74, E. Germany) Schaps, P.; Hauptmann, C. *Zentralbl Allg Pathol* 120(6): 512-526; 1976.

Thirty-four pituitary adenomas were studied by light and

electron microscopy. This tissue was fixed in formaldehyde or Bouin's soln and embedded in paraffin; the slides were stained with hematoxylin-eosin, Glodner's method, PAS reaction or Herlant's tetrachrom. The adenomas were classified as chromophilic or chromophobe tumors. Twenty-seven adenomas gave intense or weak staining. Electron microscopy revealed that all adenomas contained secretory granules more or less densely packed within the cytoplasm. The number of these granules strongly correlated with the tinctorial properties of the tumor tissue. Of 11 acidophilic adenomas, 10 consisted of typical somatotrophic hormone (STH) cells. Four acromegalic patients possessed heavily or poorly granulated STH cell adenomas. One patient with a clinical history of liver cirrhosis and gynecomastia was observed bearing an acidophilic adenomatous hyperplasia of prolactin cells. Thirteen tumors consisted of cells exhibiting almost weak amphophilic staining properties and secretory granules of 100-250 nanometer diameters. One of the patients demonstrated the typical Cushing's signs. Three adenomas with PAS-positive tumor cells were judged to be composed of gonadotropic cells. Only seven adenomas did not give any chromophilic reaction. The tumors consisted of extreme poorly granulated cells which could not be significantly associated with one of the pituitary hormones by their morphological properties. On the basis of mitochondria, four of the adenomas were designated as oncocytic tumors. (47 refs.)

77-0511 Thyroid Autonomy (Plummer's Disease) with Contralateral Malignancy: Mere Coincidence? (Eng.) Wiener, J. D. (Dept. Medicine, Free Univ. Hosp., Onze Lieve Vrouw Gasthuis, Amsterdam, The Netherlands) *Acta Med Scand* 200(6): 509-512; 1976.

A case is reported of a 38-yr-old woman with an autonomous hyperfunctioning nodule in the left lobe (Plummer's disease) and a papillary carcinoma in the right lobe of the thyroid gland. T₃ (triiodothyronine) hyperthyroidism had been indicated, and no history of radiation therapy could be elicited. The right nodule was well-encapsulated by a fibrous pseudocapsule, and both nodules showed a fluent transition from normal to more pleomorphic follicular epithelium. The findings suggest that autonomy could be a stage in the progression toward malignancy. Published incidences of malignancy in Plummer's disease seem to vary with factors such as geographical differences. (21 refs.)

77-0512 Non-medullary Thyroid Carcinoma in Patients with Parathyroid Adenoma. (Eng.) Kairaluoma, M. I. (Dept. Surgery, Univ. Oulu, Oulu, Finland) Heikkinen, J.; Mokka, R.; Huttunen, R. *Acta Chir Scand* 142(6): 447-449; 1976.

Two cases are reported of patients with concomitant papillary (nonmedullary) thyroid carcinoma and parathyroid adenoma. Both patients were admitted with previously diagnosed hyperparathyroidism; the carcinoma was found inci-

dentally at operation. In case 1, a 59-yr-old farmer, an intralobar thyroid tumor showed cervical lymphatic invasion; prolonged hypercalcemia may have been an etiologic factor. Case 2, a 44-yr-old iron-plate worker, had received irradiation 16 yr earlier for cervical tuberculous adenitis. (8 refs.)

77-0513 Effects of Thymectomy in Human Oncogenesis. (Eng.) Bramis, J. (Dept. Surgery, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029) Papatestas, A. E.; Sloane, C.; Jenkins, G.; Aufses, A. H. *J Surg Res* 22(3): 305-312; 1977.

Factors that seem to influence cancer risk in women with myasthenia gravis (MyG) are the presence or absence of the thymus, thymic pathology, and interval from thymectomy. The past, present, or future development of an extrathymic neoplasm was also taken into consideration. Serum immunoglobulins (Ig) were determined in 175 women with MyG, 154 with no extrathymic neoplasms and 21 with extrathymic neoplasms. Serum IgA concentrations were lower in patients with thymomas or extrathymic neoplasms than in patients with nonthymomatous MgG who had no associated extrathymic neoplasms. In the latter group, low serum IgA levels were noted in patients with thymic tumors. The observed decrease of IgA in these patients was significant compared to controls or MyG patients with no thymic tumors. Decreases in serum IgA preceded the clinical appearance of neoplasms by many years (1-11), and, therefore, the differences could not be attributed to the presence of tumor. The level of 250 mg/100 ml was the differentiating point between patients with and without associated tumors. Differences between these two groups were noted before and after thymectomy. Serum IgA levels increased gradually with time after thymectomy, but there was a corresponding decrease in IgM. Changes in IgA following thymectomy appeared after a considerable delay. It is concluded that serum levels correlate not only with the risk of neoplasia but also with prognosis in patients with breast cancer. Neoplasms following thymectomy occurred in patients in whom these changes were not apparent. (37 refs.)

77-0514 Extramedullary Plasmacytoma of the Head and Neck, Parotid and Submandibular Salivary Glands. (Eng.) Pahor, A. L. (Dept. Otorhinolaryngology, Dudley Road Hosp., P.O. Box 293, Birmingham B18 7qH, England) *J Laryngol Otol* 91(3): 241-258; 1977.

Data from the Birmingham (England) Regional Cancer Registry show that extramedullary plasmacytoma (EMP) was diagnosed in 22 patients during the period 1963-1972. The case histories of five patients (4 men, 1 woman; 37-69 yr old) with EMP of the head and neck, including parotid and submandibular salivary glands, are presented. With respect to the 22 patients, there was an overall ratio of men to women of > 3:1 and a 5-yr survival of 60.4% for head and neck EMP and 50% for all sites. In order to diagnose EMP, it is neces-

sary to rule out multiple myeloma. Radiotherapy is the treatment of choice, after which surgery may be required to remove residual disease. Clinical response to chemotherapy is usually good. Follow-up should be life-long, because a certain proportion of EMP cases progress to multiple myeloma after a variable period of time. (23 refs.)

- 77-0515 Nuclear Tubulofilamentous Inclusions in VIPomas (Letter to Editor).** (Eng.) Leclerc, J. P. (Dept. Pathology, Hopital Lariboisiere, Paris 75010, France) Scotto, J. M. *Lancet* 1(8011): 610; 1977.

The electron microscopic study of three cases of Verner-Morrison syndrome with vasoactive intestinal peptide-secreting tumors of the pancreatic islets is reported. The cellular proliferation could be classified as D1 cells. The small (150-250 nanometers, nm) secretory granules were round, with a dense core and a tightly fitting limiting membrane. Some nuclei lodged tubulofilamentous inclusions (max length 5,900 nm) crossed by regularly spaced electron-dense material. These findings accord with a neural origin for endocrine pancreatic cells. (2 refs.)

- 77-0516 Rhabdomyoma of the Heart. Ultrastructural Study of Three Cases.** (Eng.) Silverman, J. F. (Div. Surgical Pathology, Medical Coll. Virginia, Virginia Commonwealth Univ., Box 911, Richmond, VA 23298) Kay, S.; McCue, C. M.; Lower, R. R.; Brough, A. J.; Chang, C. H. *Lab Invest* 35(6): 596-606; 1976.

The ultrastructural features of primary cardiac rhabdomyoma were studied in three infants (5 wk-8 mo of age). Light microscopy of the hematoxylin-eosin stained paraffin sections showed similar findings of well-circumscribed, poorly encapsulated to unencapsulated nodules composed of large, round, and oval extremely vacuolated cells with oval or round, central or peripherally situated nuclei with well-defined cell membranes. Occasional "spider cells" were observed, characterized by a nucleus enclosed in a central cytoplasmic mass suspended by cytoplasmic strands compartmentalizing the peripherally located vacuoles. PAS with and without diastase confirmed that the vacuoles contained intracellular glycogen. With hematoxylin-eosin, a rare cell demonstrated faint cross-striations that were usually located in the peripheral part of the cell. However, Masson's trichrome and phosphotungstic-hematoxylin showed distinct cross-striations with the characteristic "staircase" effect. No matchstick or jackstraw crystals were observed. Although the nodules were well-circumscribed, an occasional portion of the tumor projected into the surrounding cardiac muscle. Two small, poorly circumscribed, microscopic foci of rhabdomyoma cells were found in the uninvolved cardiac muscle of the 8-mo-old infant. Electron microscopy demonstrated distinct striated muscle fibers in all three cases. In the first, fibers with well-defined Z bands were prominent. The ar-

range of the fibrils was disorderly and appeared to be made up of myosin filaments up to 100 Å thick. Spacing between these filaments measured 200 Å. The A and I bands were indistinct. The other cases showed distinct, thick (120-150 Å) and thin (50-70 Å) filaments with well-formed Z, I, A, and H bands and even an indistinct M band. All three cases had considerable glycogen deposits in the sarcoplasm. Desmosomal attachments (maculae adherens) were noted. Although desmosomal attachments were exclusively seen in the second and third cases, the first case had two parallel dense lines separated by a 235-Å cleft and appearing to be covered by a fascia adherens. These cellular attachments were interpreted as intercalated discs. The Z bands in the first case were spaced 1.2-1.5 µm apart and were 192-240 nanometers thick. The exact histogenesis of the lesion remains uncertain. (19 refs.)

- 77-0517 Unusual Sites of Metastases.** (Eng.) Brady, L. W. (Dept. Radiation Therapy and Nuclear Medicine, Hahnemann Medical Coll. and Hosp., 230 North Broad St., Philadelphia, PA 19102) O'Neill, E. A.; Farber, S. H. *Semin Oncol* 4(1): 59-64; 1977.

The frequency and location of unusual sites of metastases occurring in 222 patients treated over a 15-yr period are reviewed. Metastases were preterminal depending on the primary site of malignancy. Skin metastases were usually metachronous (diagnosed after primary lesion) and preterminal with a short time span between appearance and death of patient if the primary was the lungs (1.5 to 2.6 mo), cervix (3 mo), or esophagus (4.3 mo). Skin metastases from primaries of the colon, bladder, kidney, or ovary had a slightly greater time interval of 7.3 mo (ovary) to 12.7 mo. (kidney). Metastases to the gastrointestinal tract occurred infrequently; however, when manifested they were metachronous and preterminal. Carcinomas of the lung and breast were the most common sources; the duodenum, esophagus, and ileum were the most common sites attacked. Metastases to the kidney, heart, bone, soft tissues, and female genital tract were all preterminal events. However, metastases to the male genital tract had long-term survival if adequately treated. Metastases to the eye were preterminal or treatable depending on the site of the primary lesion. Thyroid metastases were preterminal if metastasizing from lung carcinoma but no serious clinical problem when originating from lymphomatous lesions. The author stress the importance of establishing the primary source of the metastasis and the extent of the metastatic lesions in the formulation of a treatment program. (6 refs.)

- 77-0518 The Surface Morphology of Normal and Malignant Rat Liver Epithelial Cells in Culture.** (Eng.) Allen, T. D. (Paterson Lab., Christie Hosp. and Holt Radium Inst., Withington, Manchester M20 9BX, England) Iype, P. T.; Murphy, M. J. *In Vitro* 12(12): 837-844; 1976.

Normal parenchymal cells cultured from the liver of 11-day-

old male Wistar rats and malignant cells from both a 4-dimethyl-amino-azobenzene-induced primary rat hepatoma and a spontaneous liver tumor from the parent rat culture were compared in their mitotic and nonmitotic states by scanning electron microscopy. Both the normal and malignant cells settled and attached in a similar manner; most of the cells were fully spread in a typical epithelial morphology. Although the malignant cells were more "dome" shaped, there was no significant difference in the cell diameters. The malignant cells had a three- to fivefold increase in microvilli over the normal cells. In both normal and malignant cells, the onset of division was correlated with an increase in microvilli; these microvilli remained until the daughter cells separated and reassumed an epithelial morphology. In arginine-deficient medium, although the normal cells retained their epithelial morphology, the surface became dominated by numerous spherical blebs. Malignant cells in the same culture became extremely dendritic. (17 refs.)

77-0519 Enhanced Tumor Growth in Chimeric Mice. (Eng.) Elbling, L. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090, Vienna, Austria) Kurata, T.; Micksche, M. *Oncology* 33(4): 157-160; 1976.

The permanent intrinsic tolerance of chimeric Swiss albino mice (SWA) and B6D2F1 mice to parenteral tissue was investigated using a Lewis lung carcinoma (LLT). Five days after inoculation of LLT cells, the body wt decreased in all mice. However, starting with day 12, the tumor-bearing B6D2F1 and chimeric mice increased in wt, while the SWA remained unchanged. Palpable tumors were not observed in any mice before day 12. On day 19 in SWA animals, no tumor was detectable, and none was detectable at sacrifice. B6D2F1 mice and the chimeras were killed on day 21 because the chimeras reached a critical point in survival. At sacrifice, the tumors in the chimeras ranged from 5 to 6 g; in the B6D2F1 mice, the range was 6 to 10 g. No relationship between coat phenotype and tumor wt was established. Metastases were present only in the lungs; B6D2F1 mice had twice as many metastatic foci as the chimeras. The tumor nodules reached about 1.5 mm in diameter and showed evidence of an inflammatory reaction and fibrosis. The popliteal and inguinal nodes showed proliferative responses without invasion in both groups. The spleen wt of the tumor-bearing animals was markedly increased at sacrifice. (19 refs.)

77-0520 Ultrastructural and Histochemical Differences in Cell Surface Properties of Strain-Specific and Nonstrain-Specific TA3 Adenocarcinoma Cells. (Eng.) Miller, S. C. (Dept. Anatomy, Harvard Univ. Medical Sch.,

Boston, MA 02115) Hay, E. D.; Codington, J. F. *J Cell Biol* 72(3): 511-529; 1977.

Strain-specific TA3-St and non-strain-specific TA3-Ha tumor cells were compared using transmission and scanning electron microscopy and histochemical and biochemical techniques. The general internal morphology of both cell lines was similar, but dramatic differences were observed in cell surface architecture, surface coat ultrastructure, and density of neuraminidase-sensitive anionic sites expressed at the cell surface. An extensive surface coat reminiscent of the "fuzz" coat of the intestinal brush border was found on the TA3-Ha cell, and it covered the numerous microvilli characteristic of this cell. The TA3-St cell did not have a morphologically distinct surface coat and the cell surface was thrown into folds from which irregular cell processes projected. After glutaraldehyde and osmium tetroxide fixation, the surface coat of TA3-Ha cells generally appeared as a network of fine filamentous material. This thick cell coat stained intensely with polycationic ferritin, most of which did not attach with neuraminidase pretreatment. No TA3-St cell coat was visible after routine preparation, but polycationic ferritin revealed a thin layer of exposed anions on the plasmalemma. A glycoprotein, epiglycanin, was found on the surface of the TA3-Ha cell, and its significance in relation to the role of viruses in the original transformation of this cell line is hypothesized. (34 refs.)

See also:

*(Rev.): 77-0004, 77-0011, 77-0021, 77-0022, 77-0023, 77-0024, 77-0032, 77-0033, 77-0034, 77-0036, 77-0042, 77-0044, 77-0053, 77-0055, 77-0066, 77-0068, 77-0077, 77-0078, 77-0080, 77-0081, 77-0082, 77-0083, 77-0084, 77-0085, 77-0086, 77-0087, 77-0088, 77-0089, 77-0090, 77-0091, 77-0095, 77-0096, 77-0097, 77-0098, 77-0099, 77-0100, 77-0101, 77-0103, 77-0194, 77-0105, 77-0106, 77-0108, 77-0109, 77-0110, 77-0111, 77-0112, 77-0114, 77-0115, 77-0116, 77-0117, 77-0118.

*(Chem.): 77-0130, 77-0150, 77-0152, 77-0161, 77-0166, 77-0167, 77-0182.

*(Phys.): 77-0191, 77-0196, 77-0198.

*(Viral): 77-0246, 77-0274, 77-0278, 77-0286.

*(Immun.): 77-0296, 77-0299, 77-0311, 77-0317, 77-0323, 77-0334, 77-0335, 77-0358, 77-0368, 77-0371, 77-0377.

*(Epid.-Biom.): 77-0523, 77-0525, 77-0530, 77-0531, 77-0532, 77-0534, 77-0542, 77-0544, 77-0545, 77-0549.

EPIDEMIOLOGY AND BIOMETRY

77-0521 **Bronchial Carcinoma in Patients with Pre-existing Unilateral Lung Disease.** (Eng.)

Yoneyama, T. (Dept. Surgery, Natl. Cancer Centre, Tokyo, Japan) Naruke, T.; Suemasu, K.; Ishikawa, S. *Thorax* 31(6): 650-651; 1976.

Primary bronchogenic carcinoma occurring in 46 patients with previous unilateral lung disease was studied. In 37 cases (80.4%) the normal lung was the site of the tumor. Pulmonary tuberculosis and pleurisy were the most frequent past pleuropulmonary diseases. All but one squamous-cell carcinoma and all five undifferentiated small-cell carcinomas (both Kreyberg group I cancers related to exogenous carcinogens) developed in the healthy lung, whereas the adenocarcinomas were evenly distributed between the two lungs. Thus, the bronchial epithelium of the normal, relatively hyperventilated lung may be more exposed to inhaled carcinogens, resulting in a higher incidence of carcinogen-induced tumors than the diseased lung. (6 refs.)

77-0522 **Asbestos and Mesothelioma Incidence in Connecticut.** (Eng.) Bruckman, L. (Air Compliance,

Monitoring, State Connecticut Dept. Environmental Protection, State Office Building, Hartford, CT 06115) Rubino, R. A.; Christine, B. *Air Pollut Control Assoc* 27(2): 121-126; 1977.

The relationship between asbestos consumption and mesothelioma incidence in Connecticut was investigated. An analysis of 133 Connecticut residents (89 men and 44 women) diagnosed with mesothelioma between 1935 and 1972 revealed that the combined sex age-adjusted mesothelioma incidence rate per 100,000 persons (both sexes) increased ten-fold since 1935, rising from 0.02 during 1940 to 1949 to 0.25 from 1960 to 1969. The estimated asbestos consumption in the state rose from 60,500 short tons during 1940 to 1949 to 109,600 short tons during 1960 to 1969. Thus, the rapid rise in Connecticut's mesothelioma incidence rate closely follows the increase in the state's cumulative asbestos consumption for a comparable time interval and suggests a linearly increasing cause-effect relationship that warrants further investigation. (26 refs.)

77-0523 **The Frequency of Dysplasia in Cases of Leukoplakia of the Oral Cavity.** (Hun.) Banoczy, J.

(Semmelweis Orvostudományi Egyetem, Konzerváló Fogászati Klinika, Budapest, Hungary) Csiba, A. *Magy Onkol* 20(4): 243-249; 1976.

The frequency of dysplasia in patients with leukoplakia of the oral cavity is discussed. Histologic study revealed epithelial

dysplasia in 120 of 500 cases (24%) clinically diagnosed as leukoplakia. A search was conducted for any correlation between age, sex of the patients and clinical type and localization of the change. The frequency of dysplasia was higher in the erosion type of leukoplakia. The highest rate of severe dysplasias was found on the tongue and lower lip. Follow-up of 68 patients indicated that, in 9 cases, there was a delay of 6.3 yr before the formation of cancer. (8 refs.)

77-0524 **Early Onset of Oral Cancer Among Women Who Drink and Smoke.** (Eng.) Bross, I. D. (Ros-

well Park Memorial Inst., Dept. Biostatistics, 666 Elm St Buffalo, NY 14263) *Oncology* 33(3): 136-139; 1976.

Data from 145 white women with intraoral cancer and 1,977 nonneoplastic controls were examined to determine the effect of drinking and smoking on the age of cancer onset. Most of the women smoked a pack of cigarettes a day or less. Light drinkers were defined as those who drank less than 30 bottles of beer/mo, 30 glasses of wine/mo, or 30 drinks of whiskey or the like/mo; heavy drinkers were defined as those who drank more than this amount. The relative age adjusted risk for mouth cancer among light drinkers and non-smokers, non-drinkers and smokers, light drinkers and smokers, and heavy drinkers and smokers were: 1.16, 3.22, 4.03, and 10.34, respectively. The corresponding risk values for tongue cancer by the same categories were: 1.35, 2.02, 3.51, and 10.87, respectively. When the effect of age shift on the chi-square value for age-adjusted relative risks for mouth cancer was examined, women who were light drinkers and smokers were susceptible to the onset of mouth cancer 12.5 yr earlier than abstainers (at the 5% probability level). Women who were heavy drinkers and smokers showed a 20-yr shift in onset even at the 1% probability level. Women who smoked but did not drink showed a 10-yr shift in age of mouth cancer onset. Similar results were obtained for women with tongue cancer, except for those who smoked but did not drink; this latter group was not significantly different from abstainers. Exposure to alcohol only did not produce any clear shifts in age of cancer onset for either mouth or tongue cancer. The combined effects of smoking and drinking appear to be particularly significant in terms of the age of intraoral cancer onset. (15 refs.)

77-0525 **Diabetes and Obesity in Patients with Adenocarcinoma Corpus Uteri.** (Ita.) Bumma, C. (I-

stituto di Oncologia, Turin, Italy) Calciati, A.; Cacciari, F. La Grotta, G.; Falda, M. *Minerva Med* 67(50): 3261-3266; 1976.

Of 94 patients with adenocarcinoma corpus uteri, 21.3% had diabetes and 42.3% were obese. Hypertension and ovaria-

or mammary neoplasia were also common. The obese and diabetic patients were more sensitive to treatment with high doses of medroxyprogesterone acetate. Obese and diabetic women should be screened for precancerous states or carcinoma of the endometrium. (18 refs.)

77-0526 **Genital Bleeding in Women Aged 50 and Over.** (Eng.) Mantalenakis, S. J. (Obstetrical Gynecological Dept., Tzanion General Hosp., Piraeus, Greece) Papapostolou, M. G. *Int Surg* 62(2): 103-105; 1977.

A retrospective study was made of the histologic findings of 1,038 dilatation and curettages performed over a 14-yr period at Alexandra Maternity Hospital on patients ≥ 50 yr who had bleeding ranging from severe to a blood-stained discharge. The median age was 59.1 yr. Malignancy was the cause of bleeding in 22.7% of the cases. The predominant malignant tumor was endometrial carcinoma, followed by cervical carcinoma. In the 522 patients 50-54 yr old, there was little difference between the two types (32 and 29 cases, respectively). However, the curve for endometrial carcinoma peaked sharply in the group aged 60-64 yr (48/178 cases). Despite the decreasing number of cases in the older groups, the malignancy rate increased from 11.9% (62/622) in the group aged 50-54 yr to 57.1% (4/7) in those ≥ 80 yr. Atrophy of the endometrium was the most frequent cause of bleeding (33.2% of all cases), followed by adenomatous and adenocystic glandular hyperplasia (27.0%). the latter appeared in 38.8% of the patients aged 50-54 yr. It is suggested that curettage endometrial sampling become a simple office outpatient procedure in all cases of irregular bleeding for the detection of endometrial carcinoma in situ. (4 refs.)

77-0527 **The Occurrence of Precancerosis of the Vulva in the Population Screening: Prevention of Vulva Carcinoma.** (Hun.) Szucs, B. (Heves Megyei Tanacs Korlat-Rendelointezete, Onkologiai Gondozo, Eger, Hungary) *Magy Onkol* 20(3): 183-187; 1976.

Of 4,772 women screened for genital cancer, one had vulva carcinoma and 56 (1.33%) had vulva precanceroses. The majority of the precanceroses were alterations associated with pruritus; they responded well to conservative treatment. Health education plays an important role in the prevention of vulva carcinoma. It is recommended that more women be screened. (24 refs.)

77-0528 **Breast Patterns (Letter to Editor).** (Eng.) Wolfe, J. N. (Hutzel Hosp., Detroit, MI 48201) *Am J Roentgenol* 128(4): 703; 1977.

Confirmation of the author's work on breast parenchymal patterns demands certain precautions and recognitions by

other investigators. One factor concerns the reproducibility of the author's classifications; with 2-3 days of intensive training, experienced radiologists with a keen interest in mammography have been able to reproduce the author's results 90% of the time. In a recently reviewed series of 514 consecutive biopsies, carcinomas were found in 104 patients. In another series randomly collected for comparison, information was available on 104 patients who had proved breast cancer at least 6 mo after a negative examination. The risk distribution between the two groups, which are tabulated, varied. Missed cancers on the first examination accounted for only a small number of these cases. The higher prevalence of cancer in two of the author's breast-type groups was most likely due to the fact that these types of breasts favor the development of a recognizable cancer. The presence of significant amounts of tissue other than fat within the breast should be an indicator of risk. Breast carcinomas do not derive from fat. They are often accompanied by desmoplasia and are of epithelial origin, the elements that form the basis of the author's classification. (no refs.)

77-0529 **The Supposed Cancer Risk from Mammography.** (Ger.) Oeser, H. (Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, W. Germany) Koeppe, P.; Rach, K. *Fortschr Rontgenstrahl* 125(6): 487-490; 1976.

Patients with tuberculosis who underwent repeated x-ray diagnostic examinations were statistically analyzed for breast cancer incidence. The results showed a nonsignificant increase in incidence in these patients compared with similar patients who did not undergo x-ray diagnoses. In addition, the curve depicting breast cancer incidence as a function of age for the general female population is nearly parallel to that depicting the increase in accumulated radiation dose due to yearly mammographic screenings over the age of 30. These data indicate that the assumption that mammography presents a cancer risk is unjustified. The view that exposure to diagnostic radiation is harmful should be considered along with the fact that aging is a major factor in breast cancer. (23 refs.)

77-0530 **Histologic Specificity of the Effect of Age at Birth of First Child on Breast Cancer Risk.** (Eng.) Morrison, A. S. (Dept. Epidemiology, Harvard Sch. Public Health, Boston, MA) *Int J Cancer* 18(6): 723-726; 1976.

The histologic specificity of the influence of age at birth of the first child on breast cancer risk was evaluated. Out of 582 slides of breast cancers examined, linear tumor strands were observed in 51.4%, areas of intraductal cancer in 24.7%, and areas of lobular carcinoma in situ in 6.9%. The relative frequencies of the three histologic characteristics were arranged according to age at first birth. The percentages with each histologic characteristic were similar for nulliparous and for all parous patients. For parous patients, the percentage of women with each feature tended to increase with age at first

birth, although there were some irregularities. The proportion with any of the three characteristics also increased with age at first birth. Adjustment for age at diagnosis had little effect on these trends. The incidence rate of tumors with linear strands was 0.7 as high for parous women as for nulliparous. Compared to nulliparous women, parous women had a low risk of breast cancer with or without linear strands or areas of intraductal carcinoma. Tumors with areas of lobular carcinoma in situ were relatively infrequent. However, parity seemed to reduce the risk of tumors without, but not of those with, this feature. Among parous women, the increase in risk with increasing age at first birth was pronounced for tumors with each of the histologic characteristics. For these tumors, first birth at age 35 or more conveyed a risk of five or more relative to first birth before the age of 20. There is only a small increase in risk for tumors with none of these characteristics. (9 refs.)

77-0531 The Pathology of Mammary Cancer and its Morbidity in the Statistical Evaluations. (Hun.)

Papoczy, A. (Orvostovábbképző Intézet, Egészségügyi Szervezési Tanszék, Budapest, Hungary) Nagy, A.; Kadar, T.; Paksy, A. *Magy Onkol* 20(3): 145-156; 1976.

One thousand one hundred fifteen patients treated for mammary cancer were statistically studied. The frequency of mammary cancer was slightly higher in the left breast than the right. The primary process was in the outer upper quadrant in nearly 50% of the cases. The diameter of nearly half of the tumors was less than 3 cm. Tumors were more frequent in women over 40. About one half the cases were stage II according to the Steintal classification. Younger patients had more metastases; 73% of the patients without metastases lived more than 5 yr. Nearly 80% of the tumors were solid. (12 refs.)

77-0532 Bilateral Carcinoma of the Breast. (Eng.) Buls, J. G. (Peter MacCallum Clinic, Melbourne, Australia) Bennett, R. C.; Chan, D. P. *Aust NZ J Surg* 46(4): 336-340; 1976.

The case records of breast cancer patients treated between 1968 and 1973 at a clinic in Melbourne, Australia, were reviewed. A total of 173 patients were found to have carcinoma in the second breast. Of these, 97 were considered metastatic lesions and 76, bilateral primary carcinomas (21 synchronous and 55 metachronous). Some patients developed the second carcinoma while under routine follow-up of the first lesion, but others presented many years after treatment of the first carcinoma. The age range of the 21 patients with synchronous carcinomas was 39-93 yr. Fourteen patients delayed with symptoms for more than 1 mo before presenting for diagnosis and treatment. Six patients gave a family history of breast carcinoma. After treatment, nine patients remained disease-free up to a max of 7 yr at the time of review. The

remaining 12 patients had evidence of recurrent disease. The period during which they remained recurrence-free ranged from 1 mo to 6 yr (av 21 mo). Nine patients died of their disease, with an av survival time of 2.7 yr. The ages of the 55 patients with metachronous carcinomas ranged from 30 to 77 yr (av 51). Twenty-eight patients complained of symptoms for periods of over 1 mo prior to presentation, and 11 patients gave a family history of breast carcinoma. The disease-free interval ranged from 5 mo to as long as 43 yr. Twenty-five patients remained free of disease up to a max period of 9 yr at the time of review. The remaining 30 patients had evidence of recurrent disease, with disease-free intervals ranging from 1 mo to 14 yr (av 35 mo). Eighteen patients had died of their disease, with an av survival time of 3.6 yr after the appearance of the second carcinoma. The significance of long-term follow-up with regular examination is emphasized. (10 refs.)

77-0533 The Magnitude of the Breast Cancer Problem. (Eng.) Cutler, S. J. (Biometry Branch, NCI, Bethesda, MD 20014) Devesa, S. S.; Barclay, T. H. C. *Rec Results Cancer Res* 57: 1-9; 1976.

Breast cancer incidence between the ages of 45-65 yr has increased from 1935 to 1972 in the United States. Different geographic areas have had different incidence rates that now appear to be converging at 70 breast cancer cases diagnosed/100,000 women/yr. Possible explanations of this convergence are that women having different risk factors are becoming more evenly distributed, or that women are becoming more homogeneous with respect to other risk factors such as age at first pregnancy or diet. The 5-yr survival rates for breast cancer are improving; reported rates are 53% for patients diagnosed in 1940-1949; 60% for 1965-1969. (4 refs.)

77-0534 Estrogen Profiles and Breast Carcinoma in Women. (Pol.) Teter, J. (Klinika Endokrynologii Instytutu Ginekologii i Położnictwa Akademii Medycznej, 00-325 Warsaw, Krakowskie Przedm. 8, m. 5, Poland) *Nowotwory* 26(4): 273-281; 1976.

The urinary estrone (E_1), estradiol (E_2) and estriol (E_3) levels in six young regularly menstruating normal women were quantitatively determined to establish the $E_3/E_1 + E_2$ ratio (index R). The mean values of the index R during the follicular and luteal phases were 1.16 and 1.24, respectively. The E_3 proportion was much higher in Polish women than in American women ($R = 1.16$ and 1.24 in Polish and 0.54 and 0.74 in American women, respectively) and the indices of breast carcinoma incidence were correspondingly lower in Poland (36 and 45) than in America (136 and 138). The estrogenic profiles in Polish women ($R = 1.16$ and 1.24) resemble those in Japanese women ($R = 1.46$ and 1.41) in the follicular and luteal phases of the cycle. In both these populations the high proportions of estriol were connected with low indices of breast carcinoma incidence (45.2 and 36.6 in Polish women).

and slightly lower in Japanese women--27.5 and 31.8). These data confirm the view that low proportions of estriol correlate with high breast carcinoma incidence. (20 refs.)

77-0535 Follow-up Study of Male and Female Offspring of DES-Exposed Mothers. (Eng.) Bibbo, M. Dept. Obstetrics and Gynecology, Univ. Chicago, Chicago, IL) Gill, W. B.; Azizi, F.; Blough, R.; Fang, V. S.; Rosenfield, R. L.; Schumacher, G. F.; Sleeper, K.; Sonek, M. G.; Wied, G. L. *Obstet Gynecol* 49(1): 1-8; 1977.

Male and female offspring of mothers who were part of a double-blind, placebo-controlled investigation during 1951 and 1952 to determine the therapeutic value of diethylstilbestrol (DES) administered during pregnancy were examined to assess the effects of DES on the genital tract. Eighteen percent of 299 DES-exposed women had irregular menstrual cycles, compared to 10% of 136 controls. The history of pregnancy in the controls was 33% in contrast to 18% in the DES-exposed group. Ridges of the vagina and cervix were seen in 91 (40%) of the DES-exposed group. Cytologic findings indicated that dysplastic lesions were also more prevalent in this group. Colposcopy of the vagina revealed adenosis in 153 (66.81%) of the DES-exposed women and in 5 (3.68%) of the controls. In 163 DES-exposed men, epididymal cysts, hypoplastic testes, and induration of the testicular capsule were more prevalent than in 168 male control offspring. Analysis of semen from 39 DES-exposed men and 25 controls showed that the av sperm density was approximately two times lower in the DES-exposed group. Ejaculate volumes of 1.5 ml were observed in 10/39 DES-exposed subjects versus 0 in controls. Quality scores for 11/39 of DES-exposed men were > 10, or severely pathologic, whereas none of the controls received this score. Pathologic semen quality could be associated with physical abnormalities. Although none of the DES-exposed patients had cancer, there seems to be a higher risk of squamous atypia in women and functional changes in the male reproductive system. Careful follow-up of women is necessary to reveal any increased risks for developing carcinoma. (18 refs.)

77-0536 ACS Commission on Cancer Survey Supports Suggested Association Between Oral Contraceptive Usage and Liver Tumors. (Eng.) Murphy, G. P. Buffalo, NY) *Bull Am Coll Surg* 62: 28, 33; 1977.

A suggested association between the use of oral contraceptives and liver tumors is supported, at least for benign tumors, according to data collected recently by the Commission on Cancer of the American College of Surgeons. A total of 528 primary malignant or benign liver tumors was reported by 120 hospitals in 46 states, of which 166 occurred in men (148 malignant and only 19 benign). Of the 362 tumors diagnosed in women, 163 were malignant and 199 were benign. A substantial difference was noted in the proportion of benign to malignant tumors among oral contraceptive users of all ages

(74.0% benign to 26.0% malignant), compared to nonusers (44.9% benign to 55.1% malignant). Hepatic cell adenomas and focal nodular hyperplasias were observed more often in the users. Ip bleeding was a presenting symptom of hepatic cell adenoma in 12% of cases. From an epidemiological point of view, the survey has stimulated some hospitals to include all primary benign liver tumors in their cancer registries. (1 refs.)

77-0537 Temporal Changes in Primary Liver Cancer in Black Goldminers from Mozambique (Letter to Editor). (Eng.) Bradshaw, E. (Cancer Res. Unit, Natl. Cancer Assoc. South Africa, South African Inst. Medical Res., PO Box 1038, Johannesburg, S. Africa) *S Afr Med J* 50(51): 2022; 1976.

It was previously reported that there was a 44% decline in the crude rates of primary liver cancer during the period 1964-1971 in black gold miners from Mozambique. The rates dropped from 80.5/100,000 man-yr in 1964 to 44.8 in 1971. Recently, the crude rates of primary liver cancer in miners from the same area were analyzed for 1972-1974, and they were found to have dropped even further, to 50% of the 1964 level. Thus, the rates of esophageal cancer in black miners from the Transkei during 1964-1974 have continued to show the same trend as those seen during 1964-1971, a slightly falling tendency, which is within the range of random fluctuation. (1 refs.)

77-0538 Herpesvirus Infection and Cervical Anaplasia--A Seroepidemiological Study. (Eng.) Choi, N. W. (Section Epidemiology and Biostatistics, Dept. Social and Preventive Medicine, Faculty Medicine, Univ. Manitoba, 750 Bannatyne Ave., Winnipeg, Manitoba R3E 0W3, Canada) Shettigara, P. T.; Abu-Zeid, H. A.; Nelson, N. A. *Int J Cancer* 19(2): 167-171; 1977.

Prenatal serum samples were collected from 23,146 pregnant women and, after a 37- to 56-mo follow-up period had been completed, 57 cases of carcinoma of the cervix were encountered. Three controls were selected for each of the 57 cases; they were taken from the study cohort and matched for age, residence, number of prior cytology smears, and date of entry into the study. The herpes simplex virus (HSV) types 1 and 2 infection status of all these women was determined by the indirect hemagglutination test (IHAT). Analysis of the results showed that, although the proportion of cases positive for HSV-2 antibody was higher among carcinoma patients than controls, this difference was not significant statistically. The av age at diagnosis was 27.0 yr. Analysis of the geometric mean titers of antibodies to HSV-1 and HSV-2 showed that women with cervical cancer had higher av titer values than the controls for both virus types and that the mean type 1 antibody titers were greater than the corresponding type 2 antibody titers among patients and controls. The relative risk value for the association between HSV-2 infection and car-

cinoma of the cervix was 2.33. A sufficiently longer follow-up, yielding a larger sample size, is needed to assess the specific role of HSV-2 infection in the development of cervical aplasia. (18 refs.)

- 77-0539 Epidemiological Problems of Gastric Cancer in Felsőszolnok.** (Hun.) Hajdu, G. (Korzeti Rendelo, Alsószolnok, Vas megye, Hungary) *Magy Onkol* 20(3): 157-162; 1976.

The incidence and possible causes of gastric cancer at Felsőszolnok, a small village in Hungary, were studied. The long-term average gastric cancer mortality amounts to 40% of all cancer-related deaths in this village, vs 20% in the district and 32% in the country. A similarly high gastric cancer morbidity was found by screening: 5/356 in the age group > 40 yr. Cancer of the large intestine was also detected. The incidence of gastric cancer is higher among men. The screening also revealed high incidences of gastric ulcer (20/1,219) and achlorhydria (approx 50%). The high gastric cancer morbidity and mortality are linked with the consumption of large amounts of alder-smoked meat, especially by men, and with irregular dietary habits. The home-smoked meat was found to contain 6.5 times more 3,4-benzopyrene than meat smoked commercially at packing houses. A significantly lower gastric cancer incidence was reported from nearby villages in Yugoslavia, where smoked meat consumption is negligible. (16 refs.)

- 77-0540 Bladder Cancer in Car Workers (Letter to Editor).** (Eng.) Baxter, P. J. (British Leyland Ltd., Cowley Assembly Plant, Oxford, England) White, W. G.; Barnes, G. M. *Lancet* 1(8007): 377; 1977.

The death certificates of all men who had died during their employment at a British car assembly plant between 1966 and 1972 were examined. There were 276 deaths from all causes, giving a standardized mortality ratio of 85%. Bladder cancer was the underlying cause of death (at age 62) in two workers, whereas 2.6 deaths were expected. These findings suggest that car-assembly workers are not at a special risk of bladder cancer. (2 refs.)

- 77-0541 The Ethnic Distribution of Primary Central Nervous System Tumors: AFIP, 1958 to 1970.** (Eng.) Fan, K. J. (Dept. Pathology, Howard Univ. Coll. Medicine, Washington, DC.) Kovi, J.; Earle, K. M. *J Neuropathol Exp Neurol* 36(1): 41-49; 1977.

A study was made of 16,311 cases of primary CNS tumors diagnosed at the Armed Forces Institute of Pathology (AFIP), Washington, DC, from 1958 to 1970 to compare the distribution of tumors between American Negroes and Caucasians. The ratio of total Caucasian and Negro cases (C:N) was 13.7:1, or considerably higher than the US C:N

population ratio (8.4:1). Glioblastoma multiforme was the most common individual tumor in this series. Gliomas were significantly more frequent in Caucasians than in Negroes ($p < 0.005$), but Negroes had a relatively high frequency of pituitary adenomas ($p < 0.01$). Proportional frequencies of meningioma, hemangioblastoma, and nerve sheath tumors were also slightly higher in Negroes. A comparison of tumor distribution patterns between American and African Negroes (using a composite African series, 1953 to 1971) revealed a similarly high frequency of pituitary adenoma and meningioma, along with a paucity of glioma in African Negroes. The distribution of all primary intracranial and intraspinal CNS tumors according to histologic type, age, and sex is also discussed. Results indicate the important role of genetic influences in the development of at least some primary CNS tumors. (24 refs.)

- 77-0542 Hodgkin's Disease in Siblings.** (Eng.) Grufferman, S. (Dept. Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115.) Cole, P.; Smith, P. G.; Lukes, R. J. *N Engl J Med* 296(5): 248-250; 1977.

An incidence survey in Greater Boston during 1959-1973 was used to estimate the risk of Hodgkin's disease among siblings of persons with the disease. Five affected sibling pairs under the age of 45 were detected from among 1,577 persons with histologically confirmed disease. The expected number is 0.7, indicating that siblings have a sevenfold excess risk of the disease ($p=0.0008$). Records were also reviewed for an additional 1,755 persons with Hodgkin's disease, and eight more sibling pairs were identified. Among all 13 pairs, 12 were sex-concordant; the expected number is 6.8. The literature included 46 sibling pairs under 45 yr, 30 of which are sex-concordant; the expected number is 23.9. The present and literature series suggest that siblings of the same sex as an affected person have a risk of Hodgkin's disease double that of siblings of the opposite sex. The data also indicate that persons close in age to their affected sib have a higher risk of Hodgkin's disease than those more distant in age. The sex concordance suggests that the excess of Hodgkin's disease among siblings of affected persons is due either to interpersonal transmission of an etiologic agent by prolonged or intimate contact or to common-source exposures. No spouse pairs with Hodgkin's disease were found, but the study was too small to state that spouses of affected persons are not at increased risk. It is important to resolve this question, because if spouses are not at increased risk, interpersonal transmission of an etiologic agent probably does not occur, occur only before about 20 yr of age, or susceptibility is reduced after that age. (19 refs.)

- 77-0543 A Study on the Geographical Pathology of Laryngeal, Bladder and Childhood Cancer in the Province of Torino.** (Ita.) Segnan, N. (Cattedra di Epidemiologia dei Tumori Umani, Istituto di Anatomia Patologica

I dell'Universita, Torino, Italy) Tantarri, G. *Tumori* 62(4): 377-385; 1976.

The distribution of cancer of the larynx was investigated in the 12 ecological areas and/or subareas forming the non-metropolitan areas of the province of Torino. Bladder cancer in adult men and all cancers (including leukemias) in children were similarly studied. In subareas 36, 37 and 42 of the ecological area located NW of the capital and its suburbs as well as in the area located north of the province, around the town of Ivrea, a significant excess of laryngeal cancers was diagnosed in adult men between 1965 and 1969. Cancer of the bladder was found in excess in men residing in subareas 37 and 43 of the area (geographically related to the town of Cirie, where an epidemic of bladder cancer was recognized among workers of a chemical factory where 2-naphthylamine and benzidine were widely used in the past), as well as in men residing in area 02. In addition, laryngeal cancer was found in excess among residents in Balangero (where a large asbestos-chrysotile mine has been in operation for a long time) and adjacent towns. Bladder cancer was particularly frequent among residents in Cirie and adjacent towns (19 cases versus 9.18 expected) as well as in those residing in Ivrea and adjacent towns (24 versus 14.61 expected). On the contrary, the whole area situated east and south of Torino and its suburbs appeared to be a low-incidence area for both laryngeal and bladder cancer. For both tumor types the highest incidence was found in the town of Torino. Men residing in the 23 suburbs of Torino showed a high incidence of laryngeal cancer and a low incidence of bladder cancer. Cancers in children were fairly uniformly distributed throughout the province, including the capital. (9 refs.)

77-0544 **Morphology and Incidence of Childhood Tumours.** (Eng.) Marsden, H. B. (Dept. Pathology, Royal Manchester Children's Hosp., Pendlebury, England) *J Clin Pathol* 29(11): 1016-1037; 1976.

The incidence and morphology of childhood tumors were assessed from material taken from the Manchester University Children's Tumor Registry, a population-based registry started at the end of 1953 and including approx a million children under 15 yr of age. It was found that retinoblastoma and histiocytosis X occur mainly in the first 3 yr of life, and 83% of the patients with neuroblastoma in the Registry are ≤ 5 yr old. Astrocytoma is distributed throughout childhood, with the exception of pontine tumors, which occur in older children. Ependymoma is seen in younger children, and 78% occur in the first 5 yr. In the 22 yr of the Registry, no case of Burkitt's lymphoma has been included. Ten lymphosarcomas showing a prominent "starry sky" of macrophages have been seen, but the clinical picture with respect to site and leukemic transformation is different from that observed in African Burkitt's lymphoma. In black children, leukemia is relatively rare, and this applies to the black population in the US as well as to native African children. In Idaban, 4.5% of the total tumors are leukemias, compared with 30% in the

Registry. The percentage of Ewing's tumors that are PAS-positive is uncertain, but positive results with imprints stained with PAS may be seen when the findings are negative with formalin-fixed, paraffin-embedded material. As striking as the high incidence of lymphomas in African children is the relative rarity of glioma. A figure of 1.3% of tumors has been given, compared with 18% in the Registry. The juvenile type astrocytomas (81 cases) are commonly found in the cerebellum and hypothalamus. The adult type (39 cases) shows no survivors at the end of 3 yr. The order of frequency of gliomas is astrocytoma, medulloblastoma, and ependymoma. Analysis of the renal tumors in the Registry gives the following results: Wilms' tumor (82), mesoblastic nephroma (2), carcinoma (2), and angiosarcoma (1). Renal tumors account for 5.5% of the total tumors in the Registry and Wilms' tumors for 5.2%. The variation in the naked-eye and microscopical appearances of Wilms' tumor may be great with solid and cystic types. Genetic factors are apparent, particularly in the retinoblastoma. The majority of childhood tumors show a male preponderance, except for presacral teratoma. Wilms' tumor is distributed equally between the sexes. (12 refs.)

77-0545 **Melanomas of the Lower Extremity Among Native Puerto Ricans.** (Eng.) Pantoja, E. (USAF Hosp., Offutt Air Force Base, Omaha, NB) Llobet, R. E.; Roswet, B. *Cancer* 38(3): 1420-1423; 1976.

The clinical features of melanomas of the lower extremity were investigated in 57 native Puerto Ricans (35 men, 22 women, av age 63 yr). A total of 49 melanomas involved the foot, 5 the leg, and 3 the thighs. Whereas most melanomas of the lower extremity among Caucasians occur above the ankle, 86% of those in the native Puerto Rican group occurred in the foot, particularly in the minimally pigmented zones (sole, heel, and nail bed), a distribution similar to that reported in blacks. It is suggested that Negro and dark-skinned patients are especially susceptible to sunlight-induced melanomas in pigment-deficient areas. (14 refs.)

77-0546 **Trends in Morbidity on the Basis of Newly-reported Cases of Malignant Skin Melanoma (172 ICD) and Other Skin Neoplasms (173 ICD) in Czechoslovakia During the Period 1961-1972.** (Eng.) Somogyi, J. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) Hostynova, E.; Simkovic, D. *Neoplasma* 23(6): 659-665; 1976.

Trends in morbidity on the basis of newly reported cases of malignant skin melanoma and other skin neoplasms were studied in Czechoslovakia from 1961 to 1972. The morbidity rate from all malignant skin neoplasms (172 + 173 ICD) remained at almost the same level in Slovakia, but it increased in Bohemia, particularly after 1970. The morbidity growth rate expressed by the constant accretion rate proved of statistical significance for Bohemia only. The age distribution of

persons with newly reported malignant neoplasms showed considerable differences between malignant skin melanoma (172 ICD) and other malignant skin neoplasms (173 ICD). Newly reported cases of 172 ICD in persons aged 15-54 yr represented 49.1%, but those with 173 ICD in this age bracket formed only 18.6% of all the reported cases from these diagnoses. Morbidity from 172 ICD kept increasing moderately but the rate was of statistical significance only in men from Bohemia. Morbidity from 173 ICD showed a significant increase in both men and women in Bohemia, but its level in Slovakia was stable. (7 refs.)

- 77-0547 Trends in Mortality Rate from Malignant Skin Melanoma and Other Malignant Skin Neoplasms in Czechoslovakia During the Period 1921-1970.** (Eng.) Somogyi, J. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) Hostynova, E.; Simkovic, D. *Neoplasma* 23: 667-675; 1976.

A study was made in Czechoslovakia of the trends in mortality rate (per 100,000 inhabitants) from malignant skin neoplasms during the periods 1921-1937 and 1949-1970, according to differences between the sexes and between the two Federal republics Bohemia and Slovakia. Mortality from malignant skin melanoma (172 ICD) showed an evident increase after 1960, especially in Bohemia. Mortality from other malignant skin neoplasms (173 ICD) showed an overall decline after 1960, mainly due to a decline in Bohemia. In Slovakia, however, mortality from 173 ICD significantly increased in women. The effect of age of the inhabitants on mortality values is discussed. In comparison with other European countries, the ratio in Czechoslovakia of deaths from malignant melanoma (172 ICD) to the total number of deaths from all malignant skin neoplasms (172 + 173 ICD) was relatively low, although it did show an increasing trend. This ratio was lower in Slovakia than in Bohemia. Factors that may be responsible for these observed differences are briefly discussed. (7 refs.)

- 77-0548 Survival Data from a Multiphasic Mobile Cancer Detection Unit.** (Eng.) Lynch, H. T. (Creighton Univ., Dept. Preventive Medicine, 2500 California St., Omaha, NB 68178) Brodkey, F. D.; Guirgis, H. A.; Swartz, M. J.; Lynch, J. F.; Lynch, P. M. *Oncology* 33(4): 179-182; 1976.

The duration of survival of patients with cancer detected by a Multiphasic Mobile Cancer Detection Unit was assessed. A total of 5,232 patients, 1,984 men and 3,248 women, aged 18 to 90 yr, was screened. Cancer was diagnosed in 22 patients: colon (7), breast (8), endometrium (2), lung (1), prostate (1), penis (1), lip (1), and stomach (1). The 22 patients survived a total of 48.4 yr since diagnosis, as compared with an expected 38.4 yr. Only three patients have died: one each of breast, lung and stomach cancer. It is projected that the

surviving patients will live a total of 250.8 yr as against the expected 196.2 yr for later detection. (11 refs.)

- 77-0549 Occurrence of Malignant Neoplasms in Patients with Atopic Dermatitis.** (Eng.) Kaaber, K. (Dept. Dermatology, Finsen Inst., Copenhagen, Denmark) *Acta Dermatovener (Stockh)* 56(6): 445-447; 1976.

To study a possible relationship between atopic dermatitis and the development of cancer, 326 patients with this disease were followed for up to 40 yr until death or until cancer was diagnosed. Cancer occurred in 1/154 men and 8/172 women. This incidence did not differ significantly from that of the general Danish population. The two methods used to ascertain these relationships and other studies on the subject are discussed. (15 refs.)

- 77-0550 N-Nitrosamines Found in Toiletry Products.** (Eng.) Anonymous (No affiliation given) *Chem Eng News* 55(13): 7-8; 1977.

N-nitrosodiethanolamine, a compound belonging to a class of animal carcinogens, was found in a number of currently available toiletries. Investigators, using high pressure liquid chromatography and high-resolution mass spectrometry, have found the chemical--the result of nitrosation of di/triethanolamine emulsifiers by an as yet unknown nitrite compound--in approx 30 products in concentrations of 1 nanogram (ng) per g (ppb) to 48,000 ng per g. Researchers speculated that a significant amount of the chemical might be absorbed through the skin. The data was given to the Food & Drug Administration (FDA) for further evaluation. (no refs.)

- 77-0551 Causes of Death Among Construction Machinery Operators.** (Eng.) Decoufle, P. (Env. Epidemiol. Branch, A521 Landow Bldg. NIH, NCI, Bethesda, MD 20014) Lloyd, W.; Salvin, L. G. *J Occup Med* 19(2): 123-128; 1977.

Causes of death were analyzed among 2,190 deceased white male operating engineers identified from the 1967 International Union of Operating Engineers death benefit listings to explore possible risks posed by the occupational environment. Besides a threefold excess in deaths from nontransport accidents, a 125% increase in the frequency of cancer deaths, due mainly to a 30% excess in respiratory cancer deaths, was observed. There was also a 43% excess in deaths from intestinal cancer. Further examination of detailed cancer sites revealed modest increases in cancers of the genitourinary organs. Analysis of lung cancer mortality by age and the four geographic regions revealed a pattern of increasing risk with advancing age in the Northeast and West subgroups. Relative mortality from lung and genitourinary cancers was similar to the general pattern observed in workers exposed to various

coal combustion and distillation products. Cancers of the buccal cavity, pharynx, and leukemia showed low frequencies in this population. Smoking histories were not available. Further research is necessary to determine any existing cause-effect relationships. (20 refs.)

77-0552 **Cancer Deaths at Windscale.** (Eng.) Anonymous (No affiliation given) *Lancet* 1(8007): 379; 1977.

Thirteen men died from cancer while working at the British Nuclear Fuels Windscale works between 1950 and January 1975. The deaths were due to hematopoietic and lymphatic neoplasms (4 leukemias, 4 myelomas, 4 lymphosarcomas, and 1 Hodgkin's disease), all but 3 in plutonium radiation workers. The totals, however, were well below those expected.

There were no significant occurrences in the lung, liver, and bone. (1 refs.)

See also:

*(Rev.): 77-0002, 77-0009, 77-0010, 77-0012, 77-0013, 77-0014, 77-0015, 77-0016, 77-0017, 77-0018, 77-0019, 77-0020, 77-0025, 77-0026, 77-0027, 77-0029, 77-0031, 77-0039, 77-0066, 77-0078, 77-0080, 77-0085, 77-0089, 77-0097, 77-0100, 77-0102, 77-0105, 77-0113, 77-0114, 77-0118, 77-0119, 77-0120.

*(Chem.): 77-0130, 77-0131, 77-0135, 77-0166, 77-0182.

*(Phys.): 77-0186, 77-0191, 77-0196.

*(Viral): 77-0278.

*(Path.): 77-0395, 77-0420, 77-0430, 77-0442, 77-0454, 77-0465, 77-0488, 77-0496, 77-0508, 77-0514, 77-0517.

MISCELLANEOUS

- 77-0553 **Adenylate-Rich Sequences of Heterogeneous Nuclear RNA from Normal and Chronic Lymphocytic Leukaemia Lymphocytes.** (Eng.) Mansson, P. E. (Wallenberglab, Fack 7031, S-220 07 Lund 7, Sweden) Deutsch, A.; Brandt, L. *Scand J Haematol* 17(4): 276-284; 1976.

The adenylate-rich sequences of heterogeneous nuclear RNA (Hn RNA) from chronic lymphocytic leukemia (CLL) and normal lymphocytes were investigated. When a sample of the rapidly labeled high molecular wt RNA was applied to a column of poly(U) sepharose in a buffer containing 0.7 M sodium chloride and 25% formamide, 26%-52% of the total reactivity was bound to the column and could be eluted with low salt buffer containing 90% formamide. In cases of CLL, 26%-45% of the label bound to the column, but samples from normal lymphocytes bound 49%-52%. Analysis of the RNAase-resistant material demonstrated that only the poly-(U) sepharose-bound fraction [(+) Hn RNA] contained larger poly(A) segments, but both (+) Hn RNA and Hn RNA not bound to the column [(-) Hn RNA] contained short (A)-rich sequences. The levels of short and long (A)-rich regions in (+) Hn RNA expressed as percent of adenosine label corresponded to 1%-3% of the total nucleotides for short and 1.2%-2.3% for long (A)-rich regions in CLL and 1.5%-1.8% for short and 1.3%-2.0% for long (A)-rich regions in normals. The corresponding values for short (A)-rich regions in (-) Hn RNA were 1%-3% for CLL and 1.3%-1.3% for normals. Total Hn RNA contained 1%-3% of the total nucleotides as short and 0.5%-0.8% as long (A)-rich segments in cases of CLL and 1%-2% as short and 0.6%-1% as long (A)-rich segments in normals. Double-stranded regions were localized to short (A)-rich sequences. (+) Hn RNA contained 1%-2% of the label in the form of double-stranded material associated with a peak from both normal and CLL lymphocytes; however, the amount of double-stranded regions in the peak from (-) Hn RNA varied from 0.2% for normal and 0.3% for a case of relatively low WBC CLL to 3%-4% for two samples from significantly higher WBC CLL lymphocytes. Hn RNA from CLL lymphocytes contains higher amounts of the short (A)-rich fraction than that from normals. (31 refs.)

- 77-0554 **The Effect of Colony Stimulating Factor on the Synthesis of Ribonucleic Acid by Mouse Bone Marrow Cells in Vitro.** (Eng.) Burgess, A. W. (Walter and Eliza Hall Inst. Medical Res., P.O. Royal Melbourne Hosp., Parkville, Victoria, Australia, 3050) Metcalf, D. *J Cell Physiol* 90: 471-484; 1977.

^3H uridine uptake was used to study the effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) on the synthesis of RNA in cultures of mouse bone marrow, spleen, thymus, peritoneal, peripheral blood leukocytes, and lymph node cells. Cells were isolated from C_{57}BL mice. When

GM-CSF was added to cultures of mouse bone marrow cells an increase in RNA synthesis was observed. The initial stimulation appeared to be dependent on the time the bone marrow cells had been preincubated in vitro before the addition of GM-CSF. RNA synthesis was stimulated by more than 40% within 10 min of adding GM-CSF when the cultures were allowed to equilibrate 3 to 4 hr before adding GM-CSF. The maximum stimulation of RNA synthesis occurred between 10 and 12 hr after the addition of GM-CSF. After 10 hr, the stimulation of RNA synthesis was between 140% and 200%. After 20 hr, the stimulation fell to 80%. The total amount of ^3H -uridine incorporated into RNA was dependent on the cell density of the cultures. Considerably less stimulation was observed when bone marrow cells were cultured at 1×10^5 or 40×10^4 cells/ml. Stimulation was also dependent on concentration of GM-CSF in the cultures and was maximal when more than 10^4 units of GM-CSF was added per ml of culture. Actinomycin D ($0.5 \mu\text{g/ml}$) inhibited the effects of GM-CSF in bone marrow cultures. Puromycin ($100 \mu\text{g/ml}$) and cycloheximide ($100 \mu\text{g/ml}$) appeared to stimulate RNA synthesis in both control cultures and in cultures containing GM-CSF. Stimulation of RNA synthesis was not observed when GM-CSF was added to cultures of cell suspensions from thymus, subcutaneous lymph node, mesenteric lymph node or spleen. Stimulation was observed in peripheral blood leukocytes and peritoneal cells. Autoradiographic analysis showed that the effect of incubation of bone marrow cells with GM-CSF was an increase in the percentage of labeled metamyelocytes and polymorphs and an increase in their average level of labeling. (21 refs.)

- 77-0555 **Role of Hormones in Growth Kinetics of Renal Cell Carcinoma in Vitro.** (Eng.) Cummings, K. B. (Dept. Surgery/Urology, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101) Wheelis, R. F.; Nelson, F. W. *J Urol* 117(3): 269-271; 1977.

Medroxyprogesterone acetate has been used to treat metastatic renal cell carcinoma largely because of its observed inhibitory effects on the growth of estrogen-induced tumors in male Syrian golden hamsters. To examine the mechanism of action of medroxyprogesterone acetate, renal cell carcinoma tumor cells from a patient who had responded to medroxyprogesterone acetate therapy were established in tissue culture. Cells were cultured in control medium, and in the presence of therapeutic (90 nanogram/ml) and pharmacologic (9 ng/ml) levels of medroxyprogesterone acetate. Tumor cell growth kinetics were determined by the incorporation of ^3H thymidine. There was no growth inhibition affected by medroxyprogesterone acetate at therapeutic or pharmacologic levels. Therefore, the proposed salutary effect of medroxyprogesterone acetate in regression of metastatic renal cell carcinoma results from factors other than direct inhibition of renal cell carcinoma growth. (25 refs.)

77-0556 **Interaction of Two Hormones and Their Effect on Observed Rate of Initiation of DNA Synthesis in 3T3 Cells.** (Eng.) de Asua, L. J. (Dept. Cell Regulation, Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England) O'Farrell, M.; Bennett, D.; Clingan, D.; Rudland, P. *Nature* 265(5590): 151-153; 1977.

The interaction of prostaglandin F_{2a} (PGF_{2a}) and insulin and their effect on the initiation of DNA synthesis was investigated in Swiss mouse 3T3 fibroblastic cells. Addition of increasing concentrations of PGF_{2a} (0-200 nanograms, ng/ml) to the cultures caused an increasing percentage of cells to synthesize DNA in 30 hr, up to a max of 12%-23% depending on the growth medium. Addition of insulin (50 ng/ml) alone induced only 4%-5% of the 3T3 cells to synthesize DNA. Addition of insulin, however, markedly increased the response to all concentrations of PGF_{2a} up to a max labeling index of 24%-43%. PGF_{2a} with or without insulin was added to quiescent cultures, and the cumulative labeling index was followed with respect to time. Few cells became radioactively labeled in the first 15-16 hr, or lag phase, the duration of which was independent of the concentration of PGF_{2a} with or without insulin. At the end of this phase, however, the rate at which cells entered S increased abruptly, and within 2 hr the rate constant reached a steady value. Plotting of the data indicated a first-order reaction. When insulin was added 9 hr after the addition of PGF_{2a}, the kinetics of entry to the S phase were still first-order and the rate constants were similar. When insulin was added at the end of the lag phase, however, the rate constant gradually increased. After 10 hr, it was nearly the same as that for simultaneous additions, suggesting that when insulin was added near the completion of the PGF_{2a}-induced lag phase, changes in the rate constant for entry into S could be produced without appreciable delay. A single, rate-limiting step is suggested by the first-order kinetics of cellular entry into the S phase. It is possible that the interaction of PGF_{2a} and insulin upon DNA synthesis may depend on synergism upon protein synthesis. As the lag phase appears independent of serum or hormonal concentrations, the events determining its duration may be partly different from those by which hormonal concentrations determine the initiation of DNA synthesis. (21 refs.)

77-0557 **Simple Models of Nucleic Acid Interactions. I. Base-Base Interactions in 1,2-Di(adenosin-N⁶-yl)ethane and 1,4-Di(adenosin-N⁶-yl)butane.** (Eng.) Zemlicka, A. (Michigan Cancer Foundation, Wayne State Univ. Sch. of Medicine, Detroit, MI 48201) *J Org Chem* 42(3): 517-523; 1977.

The base-base interactions in 1,2-di-(adenosin-N⁶-yl)ethane (DAE) and 1,4-di-(adenosin-N⁶-yl)butane (DAB) were studied. These compounds were prepared by the same route as that for the synthesis of various N⁶-substituted adenosines from the 6-chloro-(9-B-D-ribofuranosyl)purine and corresponding amine in the presence of triethylamine in dimethylformamide. The reaction of the purine with stoichiometric

amounts of 1,2-diaminoethane gave a 30% yield of DAE, 26% recovered starting material, and 21% N⁶-(2-aminoethyl)adenosine. The condensation of the purine with N⁶-(4-aminobutyl)adenosine gave bridge nucleoside DAB in 36% yield. Nuclear magnetic resonance spectra of DAE and DAB, which supported the proposed structures, failed to reveal any information about base-base interactions. UV and circular dichroism measurements provided information about the interaction of both adenine residues in DAE and DAB. The measurements were carried out at approx 50-100 μ M, which excluded concomitant intermolecular interactions (self-association). As model compounds, N⁶-ethyladenosine was used for DAE and N⁶-butyladenosine was used for DAB. Both UV and CD spectra in water were indicative of the interaction of adenine residues in DAE and DAB. A hypochromic effect was seen in the UV spectrum of DAE together with a hypsochromic shift of the absorption max. A CD spectrum of DAE in water exhibited a profound increase in the magnitude of the Cotton effect and a bathochromic shift of its max. The hypochromism of DAE was greater than that of DAB. The increase in molecular ellipticity was greater in DAB than DAE. The data are consistent with an intramolecular base-base interaction (stacking). (26 refs.)

77-0558 **Comparison of Chromosomal Proteins of Mouse Primitive Teratocarcinoma, Liver and L Cells.**

(Eng.) Loeb, J. E. (Institut de Recherches Scientifiques sur le Cancer, CNRS, 94800 Villejuif, France) Ritz, E.; Creuzet, C.; Jami, J. *Exp Cell Res* 103(2): 450-454; 1976.

Chromosomal proteins of mouse primitive teratocarcinoma, liver and L cells are compared. The teratocarcinoma cells were a clonal culture derived from a solid tumor of the embryo-derived teratocarcinoma line OTT 6050 of 219 mouse origin. The L-M(TK-)Cl 1 D fibroblasts (L cells) were a subclone of the L permanent cell line derived from a C3H mouse. The ratio of histones to DNA (1/1) was found to be the same in teratocarcinoma cells, L cells, and liver. The ratio of nonhistone proteins to DNA was also similar in the three chromatin preparations. The electrophoretic pattern obtained at pH 3.2 in 6.25 M urea was very similar for the histones from the chromatin of teratocarcinoma, L cells and liver, except for one minor band migrating after the H₁ lysine-rich histone fraction. This minor band, present in liver, was absent in teratocarcinoma and very weak in L cells. This band corresponded to the H₀ lysine-rich histone fraction, which was found to be missing in thymus and in actively dividing cell populations. H₀ was not detected when teratocarcinoma histones were analyzed in sodium dodecyl sulfate gels under the same conditions as non-histone chromosomal proteins. Sodium dodecyl sulfate gel electrophoretograms of the non-histone chromosomal proteins contained 50-60 bands, depending upon the resolution of the gels. At first sight, the patterns appeared broadly similar. However, systematic examination revealed clear and reproducible differences between the three types of cells. Most of the teratocarcinoma bands were also found in the electrophoretograms of liver or of L cells. However, a band corresponding to 110,000 D

molecular wt was clearly more intense in teratocarcinoma than in the two other cells. There were also differences in the region between 80,000 and 60,000 D: a single marked band was found in teratocarcinoma, whereas there were two or three bands in L cells and in liver. The patterns in the region between 40,000 and 30,000 D were more similar in teratocarcinoma and L cells, while the liver pattern was completely different. A band corresponding to a molecular wt of 31,000 D was conspicuous in teratocarcinoma (M band). This M band was absent in liver and very faint in L cells. Improved methods are necessary for better characterization of the non-histone chromosomal proteins of teratocarcinoma cells. (22 refs.)

77-0559 Sister Chromatid Exchange as an Assay for Genetic Damage Induced by Mutagen-Carcinogens. II. In Vitro Test for Compounds Requiring Metabolic Activation. (Eng.) Stetka, D. G. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143) *Mutat Res* 41(2/3): 343-350; 1976.

The sister chromatid exchange (SCE) as an assay for the genetic damage induced by mutagen-carcinogens is studied. Exponentially growing Chinese hamster ovary (CHO) cells were exposed to ethyl methanesulfonate (EMS) for 24 hr at concentrations of 10^{-5} , 10^{-4} , and 10^{-3} M. Control cells were not exposed to the test chemical. The frequency of SCE per chromosome in M_2 CHO cells as a function of initial EMS concentration was determined. EMS was a potent inducer of SCE in CHO cells. Cyclophosphamide (CP) and maleic hydrazine (MH) were added to separate CHO cultures 24 hr prior to fixation at concentrations of 10^{-4} and 10^{-3} M. MH did not induce SCE's. Despite the fact that there was a significant increase in SCE frequency at the higher concentration of CP, this agent was not nearly as potent an inducer of SCE's as was EMS. When rat liver microsomes (S-9 mix) were added along with the CP, however, a significant increase in SCE frequency occurred with only a 20-min treatment. The liver extract converted CP into an active form that was very effective as an inducer of SCE's. A high concentration (1/20) of S-9 mix rendered CP even more effective at 10^{-3} M than EMS, even though the cells were exposed to CP plus S-9 for only 20 min while the EMS and/or its derivatives were present for the entire 24-hr culture period, as was CP when this drug was used without activation. Treatment with MH did not result in an increase in SCE's even with the addition of liver microsomes, indicating that this compound was not converted to a compound that will induce SCE. The results show that the in vitro SCE test for the ability to damage chromosomes can be made more sensitive to certain chemical agents by exposing cells to the compound in question together with liver microsome extract. (23 refs.)

77-0560 Development and Applications of *Bacillus Subtilis* Test Systems for Mutagens, Involving DNA-Repair Deficiency and Suppressible Auxotrophic Mutations. (Eng.) Tanooka, H. (Radiobiology Div., Natl. Can-

cer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan) *Mutat Res* 42(1): 19-31; 1977.

Bacillus subtilis test systems for mutagens, involving DNA repair deficiency and suppressible auxotrophic mutations, are developed. The hcr- strain TKJ5211 was more sensitive to 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) than the parental strain HA101 by a dose reduction factor of 5.8. Strain HJ-15, further lacking recombination and spore repair, was 50-fold more sensitive than the wild-type strains. After AF2 treatment, the His⁺ reversion sensitivity was 27-fold higher in strain TKJ5211 (hcr-1) than in strain HA101 (wild type). Similarly, dose-response curves for mutation frequency were obtained after treatment with 4-nitroquinoline 1-oxide (4NQO) and UV light. Compared with strain HA101 (wild type), strain TKJ5211 (hcr-1) demonstrated approx 25- and 20-fold increases in sensitivity for the induction of His⁺ mutations by 4NQO and UV light respectively. However, methyl methanesulfonate and x-rays gave rise to indistinguishable dose-response curves in strains TKJ5211 and HA101. Spore of strains TKJ5211 gave essentially the same results after AF2 treatment as vegetative cells. His⁺ revertants induced by the four agents in either TKJ5211 or HA101 demonstrated similar characteristics. Approx 10% of the revertants were also Met⁺, the majority of the His⁺ Met⁺ double mutant being due to suppressor mutations. In His⁺ single revertants the fraction of sus-5 phage-sensitive suppressor mutation was negligibly small. A spot test method was applied to 31 selected chemicals. Induction of mutations was detected for 10 of the 30 chemicals examined. The chemicals showing negative results by the spot test method were further tested after activation with the "S9" fraction of liver homogenates. Mutant colony counts that exceeded twice the background were positive. The S9 liver homogenate fraction nullified the mutagenic effect of AF2. The results demonstrate a somewhat broader, but almost equivalent, detection spectrum than the *Salmonella typhimurium* TA100 system. (27 refs.)

77-0561 Removal of 5-Bromo-2-deoxyuridine Incorporated in DNA of Regenerating Rat Liver (Eng.) Arfellini, G. (Istituto di Cancerologia, Università di Bologna, via S. Giacomina 14, 40126 Bologna, Italy) Prodi, G. Grilli, S. *Nature* 265(5592): 377-379; 1977.

The removal of 5-bromo-2-deoxyuridine (BUdR) from newly synthesized DNA by nuclear DNA repairing enzymes was the basis for a method of measuring DNA repair in tissue with a high DNA synthesis activity. Female Wistar rats underwent partial hepatectomy and 23 hr later (at the peak of the S phase), a mixture of ³H-thymidine (TdR) and ¹⁴C-BUdR was injected ip. Rats were killed at 1 hr-15 days after treatment and their livers were removed and processed separately. DNA was extracted and purified from the isolated nuclei using a phenol method and the radioactivity was determined after centrifugation. The double labeling was counted in a precalibrated spectrometer using two samples of DNA extracted from each of the livers. BUdR removal from DNA began 4 days after initial treatment and stopped during the

eighth day, a period in which DNA synthesis is completed and the liver mass returns to normal. The observed BUdR removal is considered an indication of DNA repair. On the basis of the radioactivity incorporated into DNA, and assuming that there was 10 picograms of DNA/cell, there were only 1.6 cell disintegrations within the first 8 days and even fewer, when it is considered that cell division occurs. The ³H/¹⁴C ratio varied when mitotic index was again low. It is possible that when BUdR is inserted into DNA, there is filament breakage similar to that which occurs rapidly in vitro after photoirradiation, and that enzymatic repair can follow. BUdR-induced breakage seems to take place more slowly than the radiation-induced process. It is suggested that the method can be used both to compare repair activity as a function of age in organs with a high DNA-synthesis activity and to study the relationship between carcinogenesis and DNA repair in systems, such as the regenerating liver, for which data are available on tumor induction by single administrations of carcinogens. (17 refs.)

77-0562 **DNA Synthesis in Rat Sarcoma and Liver: The Effect of Starvation.** (Eng.) Reilly, J. J. (Dept. Surgery, Massachusetts General Hosp., Boston, MA) Goodgame, J. T.; Jones, D. C.; Brennan, M. F. *J Surg Res* 22(3): 281-286; 1977.

Thirty-two male Fischer rats were injected sc with 1 × 10⁶ methylcholanthrene-induced sarcoma cells. By day 13, tumors were uniformly palpable. On day 20, these rats, plus 33 non-tumor-bearers, were divided into four groups: (1) non-tumor-bearing animals maintained on standard rat chow; (2) non-tumor-bearing rats allowed only water ad lib; (3) tumor-bearing animals fed as in Group 1; and (4) tumor-bearing animals starved as in Group 2. After 48 hr, they were injected with ³H-thymidine and sacrificed 2 hr later. The results confirm the "metabolic privilege" of the growing tumor during early starvation. Tumor growth proceeded unabated while the total body wt of the animal diminished. Liver DNA synthesis fell to about 20% of normal in both tumor-bearing and control animals, but ³H-thymidine incorporation into tumor DNA was increased by 50%. These experiments were conducted over a relatively short starvation- time interval, and the data may not be characteristic of the response of liver and tumor tissue to chronic depletion. (19 refs.)

77-0563 **Levels of DNA Polymerase-α and β in Normal and Xeroderma Pigmentosum Fibroblasts.** (Eng.) Bertazzoni, U. (Laboratorio di Genetica Biochimica ed Evoluzionistica del Consiglio Nazionale delle Ricerche, Via S. Epifanio, 14-27100 Pavia, Italy) Stefanini, M.; Pedrali-Noy, G.; Nuzzo, F.; Falaschi, A. *Nucleic Acids Res* 4(1):141-148; 1977.

The levels of the DNA α- and β-polymerases were determined in fibroblasts obtained from skin biopsies of normal persons and from patients with xeroderma pigmentosum

(XP) that belonged to three different complementation groups and to the variant form. The enzyme assays were performed in crude extracts and after fractionation on sucrose gradients. The levels of the α- and β-polymerases in the different cases of XP were within the same range as the control values (1 and 0.2 units/mg, respectively), and no correlation was found with severity of the disease. The sedimentation coefficients of the two polymerases from all the pathological lines were identical to those of the normal fibroblasts. It is concluded that normal human fibroblasts and fibroblasts from all the cases of XP examined contain the two main DNA polymerases previously described in human cells. The fact that the levels of both enzymes in the classical XP lines were within the normal range indicates that the repair defect is not due to a reduction in either enzyme. The defect in postreplication repair observed in the XP variant is also not correlated with any alteration in the DNA α- and β-polymerases. (26 refs.)

77-0564 **DNA Polymerases in Developing and Neoplastic Tissues.** (Eng.) Chiu, J. F. In: *Oncodevelopmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 65-74; 1976.

The distribution and activity of DNA-dependent DNA polymerases in developing rat tissues and in three hepatocellular carcinomas were investigated. In 10-day-old rat cerebella, polymerase peaks were detected around 6 to 8S (α) and 3 to 4S (β). In the cerebella of rats aged 2, 6, 10, and 16 days, the α form was active in the younger rats and decreased after the sixth postnatal day. The β form remained constant during the developmental process and maturation. In fetal and 1-wk-old rat liver, the β form and a polymerase associated with the 6S region could be detected. The 6S associated polymerase was high in fetal liver and decreased rapidly after birth. Only the β form was present in 1-mo-old and adult rats. In rats fed 3'methyl-4-dimethylaminoazobenzene (0.06% soln in laboratory meal pellets), the 6S activity appeared after about 2 wk of exposure and increased with a max between 30 and 40 days on the diet. Only the β form could be detected in rats fed α-naphthylisothiocyanate (0.05% soln in laboratory meal). The 6S form was also detected in Morris hepatomas 7777 and 3924 in large amounts along with the β form. In these hepatoma lines, the activity of 6S could be directly correlated with the degree of differentiation and growth rates. The α form of the polymerase had maximal activity at pH 7.05 to 7.5; the 6S form and the β form had optima at 7.5 to 8.0, and 9.0, respectively. (17 refs.)

77-0565 **Cyclic AMP-Dependent Protein Kinases from Normal and SV40-Transformed 3T3 Cells.** (Eng.) Gharrett, A. J. (Dight Inst. for Human Genetics, Dept. Genetics and Cell Biology, Univ. Minnesota, Min-

neapolis, MN 55455) Malkinson, A. M.; Sheppard, J. R. *Nature* 264(5587): 673-675; 1976.

The cyclic AMP-dependent protein kinases from simian virus 40 (SV40)-transformed and normal 3T3 cells were investigated. The cyclic AMP binding and protein kinase-specific activities of cytosol fractions prepared from SV3T3 and 3T3 cells were similar but not identical. The cyclic AMP binding activity (picomoles ^3H -cyclic AMP bound per milligram of protein) was 4.6 for SV3T3 cytosol and 6.6 for 3T3. The cyclic AMP dissociation constants were 2.3 nanoM for SV3T3 and 3.3 nanoM for 3T3. Cyclic AMP stimulated the SV3T3 protein kinase activity (picomoles ^{32}P incorporated per milligram of protein per minute) from 110 to 710 and the 3T3 kinase activity from 170 to 1,100. These activity ratios were about equal. Preincubation of crude cytosols at 60 C before assay for binding activity, however, indicated that the activity in 3T3 cytosol was more sensitive to heat denaturation than that in SV3T3 cytosol. After 15 min at 60 C, cyclic AMP binding activity was negligible in 3T3 cytosol, but SV3T3 cytosol still retained 25% of the activity. When SV3T3 cells were treated for 20 hr with medium containing 10^{-3} M N^6, O^2 -dibutyryl cyclic AMP (db cyclic AMP) and 0.5 mM aminophylline, the chromatographic pattern was altered. Peak 1 contained no binding activity and had an activity ratio near unity, indicating that this protein kinase was independent of cyclic AMP. An additional peak containing 35% of the total binding activity and no protein kinase activity eluted after peak 1 and before peak 2. The amount of cyclic AMP-dependent protein kinase activity in peak 2 decreased. When cytosol prepared from SV3T3 cells was treated with 10^{-4} M db cyclic AMP for 1 hr, an elution profile similar to that found after the db cyclic AMP treatment of intact cells was obtained. Elution profiles of the cyclic AMP binding and protein kinase activities after diethylaminoethylcellulose chromatography showed major differences between cytosols from transformed and normal 3T3 cells. 3T3 cytosol contained a type II cyclic AMP-dependent protein kinase, but SV3T3 cytosol contained both types I and II kinases. It is suggested that different kinase compositions result from virus transformation. (22 refs.)

77-0566 Protein Kinase Activity in Mouse Mammary Carcinoma. (Eng.) Majumder, G. C. (Indian Inst. Experimental Medicine, Calcutta-32, India) *Biochem Biophys Res Commun* 74(3): 1140-1145; 1977.

The protein kinase activity of mouse (C3H BA) mammary adenocarcinoma was studied. The specific activities of cyclic AMP-dependent (RC) and independent (C) protein kinases and a specific cyclic AMP-binding protein (R) were markedly lower in carcinoma (0.0045, 0.013, and 6.0 units/mg DNA, respectively) than they were in normal mammary cells (0.0162, 0.0682, and 17.1 units/mg DNA, respectively). Mammary carcinoma also showed much lower (1.5 units/mg DNA) specific activity of the cyclic AMP-binding protein than did normal cells (3.4 units/mg DNA), indicating a lower dependency of protein kinase activity on cyclic AMP during

neoplasia. Like normal mammary gland cells, carcinoma cells showed the presence of two protein kinase peaks (I and II), as resolved by diethylaminoethyl-cellulose chromatography. The activity of protein kinase I was independent of cyclic AMP, whereas kinase II was markedly stimulated (about five-fold) by $1 \mu\text{M}$ cyclic AMP. Chromatography profiles of the protein kinases differed with respect to normal and carcinoma cells. Kinase I and II represented about 25% and 75%, respectively, of the total activity in normal tissue and about 50% each in malignant tissue. Specific activities of kinase I and II were higher in normal cells than in carcinoma by about two- and six-fold, respectively. Thus, malignancy of the mammary gland is associated with a marked increase in the ratio of cyclic AMP-independent to dependent protein kinase. Studies with various cyclic nucleotides demonstrated that the neoplastic mammary protein kinase II, like the normal mammary enzyme, is also activated specifically by cyclic AMP. Kinase I appears to represent the catalytic subunit (C) which can be converted to the cyclic AMP-dependent form (RC) after interaction with the specific cyclic AMP-binding protein (R). The lower responsiveness to cyclic AMP for the activation of carcinoma protein kinase may thus be attributed to a higher ratio of C/RC in carcinoma than in normal cells. Altering the cyclic AMP responsiveness in the mammary carcinoma may cause a major change in the normal regulatory mechanisms in these cells. (12 refs.)

77-0567 Altered Interaction Between Binding and Catalytic Subunits of a Cyclic AMP-Stimulated Protein Kinase from Hepatoma Cells. (Eng.) Mackenzie, C. W. (Dept. Pharmacology, Univ. Minnesota, Minneapolis, MN 55455) Stellwagen, R. H. *Arch Biochem Biophys* 179(2): 495-505; 1977.

The binding activity obtained from an established line of hepatoma tissue culture (HTC) cells was investigated and found to have a lower affinity for cyclic AMP at physiological pH than the activity from normal rat liver. The apparent binding affinity of HTC preparations could be increased reversibly by adding NaCl or guanidine.HCL. In the presence of these activating substances, a macromolecular inhibitory activity was chromatographically separated from the cyclic AMP-binding activity. Removal of this inhibitory component caused the affinity of the cyclic AMP-binding activity from HTC cells to increase and resemble that observed with liver preparations. Adding the isolated inhibitory component back to HTC cells resulted in a decrease in their affinity for cyclic AMP. The inhibitory component is devoid of cyclic AMP-binding and cyclic AMP phosphodiesterase activities, has a molecular wt of 30,000, has protein kinase activity, and seems to be identical to the catalytic subunit of a cyclic AMP-stimulated protein kinase on the basis of chromatographic properties and sensitivities to heat and low pH. This catalytic subunit is a minor portion of total cellular protein kinase activity and is also present in liver extracts. The difference in the inhibitory response between liver and HTC preparations, therefore, appears to reflect differences in the cyclic AMP-binding proteins themselves. (34 refs.)

77-0568 Onco-Developmental Alkaline Phosphatase Isozymes. (Eng.) Fishman, W. H.; Nishiyama, T.; Rule, A.; Green, S.; Inglis, N. R.; Fishman, L. In: *Onco-Developmental Gene Expression*. Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 165-176; 1976.

In humans distinctive testicular alkaline phosphatase isoenzymes appear to have their counterparts in trophoblast before and after 10 wk of development. These same antigens are present in testicular teratocarcinoma and in a number of neoplastic tissues from cancer of the lung. Radioimmunoassay and immunofluorescent labeling revealed the presence of the onco-developmental gene products carcinoembryonic antigen and human chorionic gonadotropin in nonmalignant bronchial mucosa and in the established bronchogenic cancer tissue. Activation of the corresponding genes appears to be an early event in neoplastic transformation that may persist in malignancy. (8 refs.)

77-0569 Characteristics of Alkaline Phosphatase from Two Continuous Lines of Human Choriocarcinoma Cells. (Eng.) Speeg, K. V. (Gene Regulation Section, Lab. Molecular Biology, Div. Cancer Biology and Diagnosis, NCI, Bethesda, MD 20014) Azizkhan, J. C.; Stromberg, K. *Exp Cell Res* 105(1): 199-205; 1977.

The characteristics of heat stability and amino acid inhibition of alkaline phosphatase (AP) in the BeWO and Jar choriocarcinoma lines and in normal placenta tissue were investigated. Term placenta contained approx three times more total AP activity than first trimester placenta. The heat-labile enzyme of the first-trimester placenta resembled the liver or bone isoenzyme of AP rather than that of term placenta. Both tumor cell lines possessed (in varying amounts) a heat-labile AP that, on the basis of heat stability and pattern of amino acid inhibition, was similar to that of first-trimester placenta. BeWO and Jar cells also possessed an AP that was stable to heating at 65 C and was inhibited by L-phenylalanine but not by L-homoarginine. This heat-stable AP was also inhibited by L-leucine, which is a feature of the D-variant isoenzyme that occurs in approx 1% of normal placentas. The question is raised whether this enzyme is present because BeWO and Jar cells are of trophoblastic origin or because they are malignant and have undergone genome depression. There is a possible similarity in mechanisms between the appearance of heat-stable AP in term placenta and the appearance of heat-stable AP in certain malignancies. (40 refs.)

77-0570 Ectopic β -Adrenergic Receptor Binding Sites. Possible Molecular Basis of Aberrant Catecholamine Responsiveness of an Adrenocortical Tumor Adenylate Cyclase. (Eng.) Williams, L. T. (Dept. Medicine, Duke Univ. Medical Center, Durham, NC 27710) Gore, T. B.; Lefkowitz, R. J. *J Clin Invest* 58(2): 319-324; 1977.

The possible molecular basis for the aberrant catecholamine responsiveness of the adenylate cyclase of adrenocortical car-

cinoma 494 was assessed. The binding of the β -adrenergic antagonist, ^3H -dihydroalprenolol, was investigated in membranes prepared from normal adrenal and tumor tissue from male Sprague-Dawley rats. In the presence of 0.7 nanoM antagonist, 48 femtomoles of antagonist were specifically bound per mg of tumor membrane protein. By contrast, membranes from normal adrenal tissue bound only 5 femtomoles antagonist. Experiments were designed to determine whether the binding sites detected in adrenal tumor membranes had the characteristics of β -adrenergic receptors. Binding of 0.7 nanoM antagonist to 0.3 mg protein/ml of tumor membranes was rapid, reaching a steady-state level in < 5 at 37 C. Binding was constant for at least 16 min of incubation. In separate experiments, the reversibility of binding was tested by adding a large excess (10^{-5}M) of propranolol to an equilibrated mixture of antagonist and tumor membranes. The specific binding was rapidly and totally reversible. Analysis of the antagonist binding sites in the tumor membranes demonstrated that they had a high affinity for the antagonist. The number of binding sites (0.094 picomole/mg protein) on the tumor membranes was calculated. The binding displayed a typical β -adrenergic specificity. The adenylate cyclase of the tumor tissue was stimulated by ACTH, sodium fluoride, and isoproterenol. The results indicate that adrenocortical carcinoma 494 membranes contain β -adrenergic receptor-binding sites not normally present in adrenal tissue membranes. (21 refs.)

77-0571 Concomitant Elevations in Serum Sialyltransferase Activity and Sialic Acid Content in Rats with Metastasizing Mammary Tumors. (Eng.) Bernacki, R. J. (Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY 14263) Kim, U. *Science* 195(4278): 577-580; 1977.

The serum sialic acid content and sialyltransferase activity in W/Fu female rats with metastasizing mammary tumors were compared with values found in normal rats and rats with various nonmetastasizing mammary tumor. Animals with metastasizing STMT-058, DMBA-4, or SMT-2A tumors had exogenous transferase activities approx double those of control rats or rats with nonmetastasizing MT-W9B, MT-W9A, MT-66, or MT-100 tumors. Endogenous activities were low in all cases, although they were somewhat higher and more variable in serum obtained from animals with metastasizing tumors. The differences in serum transferase activity between animals with metastasizing tumors and those with nonmetastasizing tumors were larger and more easily discernible than the differences in serum sialic acid content. Both serum transferase and sialic acid began to increase in rats with the SMT-2A tumor during the third week after tumor transplantation. At this point, the tumor began to establish metastatic colonies in regional lymph nodes. At 21 days, MT-W9B was twice as large as SMT-2A. At 42 days, both primary tumors were approx the same size, but by this time SMT-2A had metastasized widely and its total vol was greater than that of MT-W9B. Liver microsomal transferase

activity either remained the same or decreased in rats after tumor implantation and became elevated over time only in SMT-2A. The transferase activity of the metastasizing tumor more than doubled between 21 and 42 days after implantation, and it was sixfold higher than that of the nonmetastasizing tumor at 42 days after implantation. Sialyltransferase may play a role in the immune escape mechanism of metastasizing tumor cells. (30 refs.)

- 77-0572 Galactosyl Transferase of a Golgi Fraction from Cultured Neoplastic Mast Cells.** (Eng.) Freilich, L. S. (Dept. Periodontics, Tufts Univ. Sch. Dental Medicine, Boston, MA 02111) Lewis, R. G.; Repucci, R. C.; Silbert, J. E. *J Cell Biol* 72(3): 655-666; 1977.

A Golgi fraction was obtained from homogeneous populations of P815 mouse mastocytoma cells and studied by electron microscopy. The density and sedimentation characteristics of the Golgi apparatus from these neoplastic mast cells are believed to be similar to those of liver Golgi apparatus, since the centrifugal densities and sucrose densities used to obtain them both were identical. The Golgi fraction from the cultured mast cells was rich in galactosyl transferase, which could thus be used as a marker enzyme. Concentrations of the acceptors ovalbumin, desialylated degalactosylated orosomucoid, and N-acetylglucosamine for optimal galactose incorporation were determined, and substrate inhibition effects were shown with the higher concentrations of all three. Manganese was necessary for galactose incorporation, a higher concentration of which afforded some protection from substrate inhibition by acceptors; however, the manganese itself was inhibitory. All three acceptors competed with one another for galactose incorporation, which indicated that a single enzyme catalyzed the transfer of galactose for all acceptors. (25 refs.)

- 77-0573 Increased Thymidylate Synthetase Activity in 5-Fluorodeoxyuridine-Resistant Novikoff Hepatoma Cells.** (Eng.) Wilkinson, D. S. (Dept. Biochemistry, Univ. South Florida, Coll. Medicine, Tampa, FL 33612) Solomonson, L. P.; Cory, J. G. *Proc Soc Exp Biol Med* 154(3): 368-371; 1977.

A 5-fluorodeoxyuridine (FUDR)-resistant Novikoff hepatoma cell line, which had been characterized previously as being thymidine kinase (tdk)-deficient, was investigated to determine its thymidylate synthetase level. There was little difference between N1-S1 cells (tdk-containing, FUDR-sensitive) and N1-S1/FUDR cells (tdk-deficient, FUDR-resistant) in the levels of deoxycytidylate deaminase or ribonucleotide reductase. However, there was a significant increase in thymidylate synthetase activity in the N1-S1/FUDR cells. The sensitivities of the thymidylate synthetase from both tumor cell types to inhibition by fluorodeoxyuridylate (FdUMP) were the same. At equal protein concentrations, FdUMP, at a final concentration of 5×10^{-6} M, inhibited the thymidylate synthetase activity in both the N1-S1 and

N1-S1/FUDR cell-free extracts by > 98%. The specific activity of $(\text{Na}^+ + \text{K}^+)$ -ATPase in N1-S1/FUDR cells was only one-fifth that present in N1-S1 cells, but there was little difference in 5'-nucleotidase activity. The thymidylate synthetase activity in the FUDR-resistant cell line is sensitive to inhibition by FdUMP to the same extent as the FUDR-sensitive line. (21 refs.)

- 77-0574 Gene Expression of Branched Chain Amino Acid Transaminase Isoenzymes During Cellular Differentiation and Carcinogenesis.** (Eng.) Ichihara, A.; Goto, M.; Tomita, Y. In: *Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 723-726; 1976.

The genetic expression of branched chain amino acid transaminase isoenzymes during cellular differentiation and carcinogenesis was investigated. In normal tissues, enzyme I appeared in all tissues examined, Enzyme II in only adult liver, and Enzyme III in brain, ovary, and placenta. Enzyme III also appeared in rapidly growing hepatomas, indicating that it was a carcinoplacental antigen. Since enzyme II was not present in the fetal liver, it could be regarded as a marker of mature liver. The pattern in human tissues was similar except that human liver contained no enzyme II, and all tissues contained a small amount of enzyme III; enzyme III was also observed in human cancers. When rat hepatocytes were transformed in culture by chemical carcinogenesis or long-term culture, they acquired enzyme III; chromosomal numbers varied from the diploid figure. Therefore, acquisition of enzyme III and deletion of enzyme II in transformed cells appeared to be caused by a change in gene expression during carcinogenesis. Enzyme III was also observed in Morris hepatoma 7316A after long periods in culture; the modal chromosome number also changed during this period. Studies with protein turnover in normal and transformed cells suggest that the mechanisms regulating the intracellular concentrations of proteins in growing and nongrowing cells may be different. (8 refs.)

- 77-0575 Cellular Localization of a Carcinofoetal Enzyme (Aldolase C) and of the Normal Adult Enzyme (Aldolase B) in Fast-Growing Rat LF Hepatomas.** (Eng.) Hatzfeld, A.; Feldmann, G.; Frayssinet, C.; Schapira, F. In: *Onco-Developmental Gene Expression.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): pp. 185-190; 1976.

Aldolase C from rat brain and aldolase "C" from fast-moving hepatomas induced by 4-dimethylaminoazobenzene were purified. Biochemical methods showed that the enzymatic and physicochemical properties of pure aldolase C from brain and from LF hepatomas are the same. Using an immunoperoxidase technique, aldolases B and C were localized

a fast-growing hepatoma cells. The morphology of the cells synthesizing aldolase B or aldolase C appears to be the same. It is hypothesized that the abnormal expression of normal brain aldolase C by the genome of cancerous liver results not from cellular selection, but from the disturbance of protein synthesis regulation in hepatoma cells. (11 refs.)

77-0576 Different Cation Requirements for Aggregation of BHK Cells and Their Transformed Derivatives. (Eng.) Urushihara, H. (Lab. Cell Differentiation and Morphogenesis, Inst. Biophysics, Faculty Science, Univ. Kyoto, Kyoto 606, Japan) Takeichi, M.; Hakura, A.; Okada, C. S. *J Cell Sci* 22(3): 685-695; 1976.

The adhesive properties of normal and polyoma-transformed BHK (pyBHK) cells were examined with respect to their cation requirements. BHK cells singly dissociated by trypsin aggregated in a medium with Ca ions, but not in a medium with Mg ions. However, pyBHK cells, after dissociation with trypsin, aggregated equally well with either ion. When EDTA was used for the dissociation of cells from culture on a substrate, neither BHK nor pyBHK cells required the addition of divalent cations to the medium for rapid aggregation. Trypsin-dissociated BHK cells aggregated in a medium containing Ca ions before aggregation. With pyBHK cells, incubation in a medium with either Ca or Mg ions was effective. Ca and Mg ions are equally effective for adhesion of both BHK and py BHK cells to a noncellular substrate or to a cell monolayer. The existence of two different mechanisms for cell adhesion, one Ca-dependent and the other Mg-dependent, was previously proposed. These results suggest that only the Ca-dependent mechanism is well-developed in BHK cells, but both mechanisms are present in pyBHK cells. It has also been suggested that tryptic digestion for dissociating cells damages key molecules at the cell surface or modifies their arrangement on the surface, altering the adhesive properties of the cells. The present results seem to substantiate such a view, since previous incubation is necessary to render trypsinized cells adhesive. (23 refs.)

77-0577 Neoplastic Potentials and Regulation of Uptake of Hexose and Amino Acid Analogues in the Neoplastic GIV Line. (Eng.) Kalckar, H. M. (Section Cell Metabolism, John Collins Warren Labs., Huntington Memorial Hosp., Harvard Univ., Massachusetts Gen. Hosp., Boston, MA 02114) Christopher, C. W.; Ullrey, D. *J Cell Physiol* 89(4): 765-767; 1976.

Some aspects of transport regulation in the glutamine-independent variant (GIV) of the polyoma-transformed BHK fibroblast line 6 (BHK Py6) were examined. The transport and uptake rates of cycloleucine, 2-deoxyglucose and galactose into GIV cultures raised in the absence of glutamine were compared with those for the same type of cultures after 20 hr exposure to glutamine. The estimates were also compared with the rates of the parental culture Py6 grown in

ordinary medium and an untransformed BHK line. In the GIV strain, a downward regulation of hexose uptake was not accompanied by a downward regulation of the transport of amino acid analog but by an upward regulation, especially of cycloleucine. Exposure of the GIV strain to glutamine stimulated the abnormally low uptake rates of 2-deoxyglucose and galactose and moderated the high rates of cycloleucine transport. GIV cells that were exposed for 24 hr to growth medium containing glutamine and subsequently to medium devoid of glutamine for the same period of time behaved as if they had never been exposed to glutamine. The subsequent exposure to glutamine-free medium brought about a sharp rise in cycloleucine transport and a fall in the hexose uptake systems. This indicates that the peculiar inverse type of regulation can be modulated in both directions. The same type of modulations, although not as marked, can also be observed by using leucine or α -aminoisobutyric acid as substrates. (3 refs.)

77-0578 Phosphate Transport and Its Relationship to Cation Movements in Ehrlich Lettre Ascites Tumor Cells. (Eng.) Mazumder, A. (Dept. Experimental Biology, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY 14263) Wenner, C. E. *Arch Biochem Biophys* 179(2): 409-414; 1977.

The mechanism and regulation of inorganic phosphate (P-i) uptake by ascites tumor cells was studied by comparing the incorporation of ^{32}P -i into Ehrlich Lettre mouse ascites cells when competitive anions and inhibitors that alter cation movements were present. Sulfanilate (35 mM) and succinate (30 mM) decreased ^{32}P -i uptake by 35%, suggesting that transport is mediated by a protein similar to the 100,000-molecular-wt anion carrier isolated from RBC membranes. Furosemide, a diuretic that bears a structural analogy to sulfanilate inhibitors of anion transport, also decreased ^{32}P -i incorporation at concentrations as low as 2×10^{-5} M. This inhibitor blocks cation exchange in ascites tumor cells. It is suggested that furosemide sensitive cation exchange protein may function to facilitate anion transport. Ouabain, which inhibits $(\text{Na}^+ + \text{K}^+) \text{-ATPase}$ and its dephosphorylation, stimulated the rate of incorporation of ^{32}P -i into cells and raised the net inorganic phosphate level. The stimulation of ^{32}P -i incorporation was decreased by sulfanilate or succinate. Addition of 10 mM K^+ , which stimulates $(\text{Na}^+ + \text{K}^+) \text{-ATPase}$ and its dephosphorylation, decreased ^{32}P -i incorporation. The results indicate that the transport of P-i by intact ascites tumor cells involves a passive transport across the plasma cell membrane and an energy-dependent P-i uptake by tumor cell mitochondria. (18 refs.)

77-0579 Purine Transport in Cultured-Normal and Mouse Sarcoma Virus-Transformed Rat Kidney Cells. (Eng.) Joy Yang, Y. H. (Dept. Biochemistry, Univ. Southern California, Sch. Medicine, Los Angeles, CA 90033) *Biochem Med* 17(1): 87-98; 1977.

Differences in the transport of adenine, guanine, and hypoxanthine between normal rat kidney cells (NRK) and NRK cells nonproductively transformed (TRK) by Kirsten mouse sarcoma virus were investigated. Low concentrations of substrate and short incubation periods (2 min) were used, conditions in which transport is rate-limiting. Adenine and hypoxanthine were transported by saturable and nonsaturable processes in both cell types. The nonsaturable process for adenine and hypoxanthine uptake (2.5 and 1.3 picomoles/mg protein/min/ μ M external concentration, respectively) was similar in both lines. The apparent K_m and V_{max} values for the facilitated transport of both purines were over two times higher for TRK cells than for NRK cells. Uptake by NRK cells was greater at extracellular concentrations of adenine and hypoxanthine $< 30 \mu$ M, but uptake by TRK cells was greater at concentrations $> 30 \mu$ M. Guanine uptake was slightly greater in the NRK cells at all concentrations tested. The structural requirements for adenine transport were specific in both lines, as indicated by the inability of uric acid, hypoxanthine, and several purine analogs to inhibit adenine uptake. This was also observed for the other two purines, but to a lesser extent. The differences in uptake of the three purines between the two cell lines demonstrate that viral transformation induces changes in transport properties. Extracellular concentrations of purines and purine analogs may have a strong influence on the relative amount of purines transported by the different cell types. (10 refs.)

- 77-0580 Plasma Membrane Intramembranous Particle Topography in 3T3 and SV3T3 Cells: The Effect of Cytochalasin B.** (Eng.) Scott, R. E. (Lab. Membrane Pathology, Dept. Pathology and Anatomy, Mayo Clinic/Foundation, Rochester, MN 55901) Maercklein, P. B.; Furcht, L. T. *J Cell Sci* 23: 173-192; 1977.

Plasma membrane intramembranous particle (PMP) topography was examined by freeze fracture and electron microscopy in large samples of 3T3 and simian virus-transformed 3T3 cells (SV3T3) prepared by several methods. SV3T3 cells showed a more random topography in all preparative schemes. The av extent of PMP aggregation was 15% (8%-24% range) for SV3T3 cells, but for 3T3 cells it was 70% (range 60%-93%). Studies with cytochalasin B (CB) showed that it promotes PMP disaggregation in 3T3 cells and does not significantly affect SV3T3 membranes. CB was most effective at 1-500 nanograms/ml, and its effect was reversible. The results of these experiments support the hypothesis that CB has a high dose effect on microfilaments and a low dose effect on the plasma membrane. (37 refs.)

- 77-0581 Effects of Trypsin on the Platelet-Aggregating Activity of Mouse Tumor Cells.** (Eng.) Gasic, G. J. (Dept. Pathology, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19174) Gasic, T. B.; Jimenez, S. A. *Thromb Res* 10(1): 33-45; 1977.

The effects of trypsin on the activity of a platelet-aggregating (PA) factor found in 15091A and MCA6 ascites mouse tumor cells were evaluated. Untreated 15091A cells (5×10^5 to 1×10^6 cells) and MCA6 cells (5×10^5 cells) induced PA. A PA factor was also found in cell-free supernatants released spontaneously by these cells. However, upon trypsinization, using three different methods, this factor disappeared from the cells. Its recovery in the cell-free supernatant depended on the degree of trypsinization. The activity of the cells was restored completely after an 18-hr incubation in trypsin-free medium. This recovery was initially more rapid for the MCA6 cells, with some activity being detected after 4 hr. The two protein-synthesis inhibitors, cycloheximide and puromycin (10μ g/ml) prevented the recovery of PA. Cell-free supernatants, whether trypsin digests or material shed spontaneously by undigested cells, also induced PA. This nondialyzable material was sensitive to heat and trypsin. These data and those of others show that the active factor responsible for PA is a protein or protein complex. (22 refs.)

- 77-0582 Metabolic Co-operation in HGPRT+ and HGPRT- Embryonal Carcinoma Cells.** (Eng.) Hooper, M. L. (C.R.C. Cell Genetics Group, Insts. Genetics and Virology, Univ. Glasgow, Church St., Glasgow G11 5JS, Scotland) Slack, C. *Dev Biol* 55(2): 271-284; 1977.

The metabolic cooperation in hypoxanthine-guanine phosphoribosyltransferase (HGPRT)+ and HGPRT- embryonal carcinoma cells was studied. The clones were isolated from the mouse line PC13. Autoradiographs prepared from PC13 cultures incubated 6-24 hr with 3 H-hypoxanthine showed a uniformly heavy silver grain deposit in the emulsion overlying individual cells. By contrast, pure cultures of PC13TG8 cells (the karyotype of one HGPRT- clone) demonstrated only one or two grains per cell. With cocultures of PC13 and PC13TG8 cells in a ratio of 1:20, most cells showed little incorporation of label into trichloroacetic acid-insoluble material, but approx 5% of the cells, presumably PC13 cells, were heavily labeled. The PC13 and PC13TG8 lines demonstrated metabolic cooperation with each other and with Chinese hamster Don cells, but not with derivatives of mouse L cells. Both also showed a significant degree of chromosome imbalance, and they possessed a marker isochromosome. (1 refs.)

- 77-0583 Chloride-Stimulated Sulfate Efflux in Ehrlich Ascites Tumor Cells: Evidence for 1:1 Coupling.** (Eng.) Villereal, M. L. (Dept. Physiology, Univ. Texas Health Science Center, San Antonio, TX 78284) Levinson, C. *J Cell Physiol* 90: 553-564; 1977.

An inhibitor of sulfate transport, 4-acetamido-4'-isothiocyano-stilbene-2,2'-disulfonic acid (SITS), was used to define the stoichiometry of chloride-stimulated sulfate efflux in Ehrlich ascites tumor cells. In tumor cells equilibrated in

5 mM SO_4^{2-} medium free of Cl^- and then placed in SO_4^{2-} free, 25 mM Cl^- medium, the net uptake of Cl^- is greater than the loss of SO_4^{2-} . SITS (2×10^{-4} M) almost completely inhibited the efflux of SO_4^{2-} but had no effect on the influx of Cl^- . The lack of effect of SITS on Cl^- uptake and the differences in the rate and magnitude of Cl^- uptake compared with SO_4^{2-} loss suggest that a Cl^- permeability, pathway distinct from that of SO_4^{2-} , exists. The addition of furosemide, Cl^- transport inhibitor, inhibited the uptake of Cl^- by 94% but had no effect on Cl^- stimulated SO_4^{2-} efflux. When a combination of furosemide and SITS was used, a linear relationship between SITS sensitive Cl^- uptake and SO_4^{2-} loss was discovered. The slope to the line indicated that one SO_4^{2-} exchanges for one Cl^- . The uptake of Cl^- was accompanied by an increase in cellular Na^+ , which maintains the electroneutrality of the cell. The results support the assertion that the tumor cell possesses a transport system, which facilitates the exchange of one SO_4^{2-} for one Cl^- . When anion transport not inhibited the stoichiometry is hidden by a second pathway for the uptake of Cl^- ; this pathway is SITS insensitive. (9 refs.)

77-0584 **Inhibitors of Polyamine Biosynthesis. 4. Effects of α -Methyl-(\pm)-ornithine and Methylglyoxal Bis(guanyldihydrazone) on Growth and Polyamine Content of L1210 Leukemic Cells of Mice.** (Eng.) Newton, N. E. (Coll. Pharmacy, Univ. Minnesota, Minneapolis, MN 55455) Abdel-Monem, M. M. *J Med Chem* 20(2): 249-253; 1977.

The influence of methylglyoxal bis(guanyldihydrazone) (MG) and α -methyl-(\pm)-ornithine(MO) on polyamine content and growth of L1210 leukemic cells of mice was investigated. Incubation of L1210 cells in the presence of MO (1-8 mM) produced a decrease in the cellular levels of putrescine and spermidine but a slight increase in the levels of spermine. Concentrations of 2 mM or more of MO decreased putrescine levels so that they were not detectable. Spermidine levels decreased from 258 picomoles/ μg DNA in the absence of inhibitor to 122 picomoles/ μg DNA in the presence of 4 mM MO. The effects of MO on the cellular polyamine levels of L1210 cells in culture were not accompanied by a decrease in growth rate, since there was no decrease in the concentration of DNA in the cell culture. Addition of MG (1-8 μM) to L1210 cells produced a concentration-dependent decrease in the number of cells, as indicated by a decrease in DNA concentration. Putrescine levels were increased 16-fold at the lowest concentration of MG used (1 μM) and fell progressively with higher concentrations. At 1 μM , MG produced an approx 50% decrease in the cellular levels of spermine and spermidine. The decrease in the levels of the amines was max at this low concentration of MG. Decreases in the total pool of polyamine nitrogen did not appear to be significant in controlling cell growth, as 4 mM MO produced a 30% decrease in total polyamine nitrogen with no decrease in DNA synthesis. In addition, in the presence of the highest concentration of MG (8 μM), the total amount of nitrogen in the polyamine pool was similar to that in the untreated cells, although there was a large decrease in the DNA content of the cell suspen-

sions. The results do not exclude a causal relationship between cell growth and cellular levels of polyamines. (28 refs.)

77-0585 **Fusion Experiments with Human Tumour Cells.** (Eng.) Watkins, J. F. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (J. F. Lehmanns Verlag: Munich): pp. 177-180; 1976.

Preliminary results from experiments aimed at establishing hybrid cell systems for the study of the somatic cell genetics of human tumor cells are presented. Thirteen human tumors (carcinoma of the bladder, parathyroid gland, breast, colon, and vulva as well as glioma and melanoma) were fused with primary kidney cells from inbred CBA mice. During periods of incubation of up to 6 mo, there was no evidence of hybrid cells growing more rapidly than the mouse kidney cells, with one exception. In one experiment, a single rapidly growing colony of transformed appearance was observed 11 wk after fusion of cells from a carcinoma of the colon. This colony showed mixed hemadsorption with a rabbit antiserum against human fibroblasts. The cells of this line were carrying a virus which banded on sucrose density gradient equilibrium centrifugation at a density of 1.23, the same density as that of the Sendai virus. The virus was cytopathogenic for primary CBA mouse kidney cells. Other fusion experiments were done with 3T3 cells (mouse fibroblasts). Many hybrid metaphase spreads and 3T3 cell metaphase spreads were seen in a fusion experiment with thyroid carcinoma cells; it was impossible to separate a hybrid clone from the background of 3T3 cells. Experiments were also performed with CBA mouse kidney cells transformed with SV40 virus. Two fusion experiments using a mutant clone which was resistant to thioguanine, one with cells from carcinoma of the rectum and the other with a primary culture of melanoma cells, both produced hybrid colonies within a few weeks. Recent fusion cultures made with carcinoma of the colon and breast contained actively growing cells with some morphological characteristics of hybrid cells. The SV40-transformed CBA mouse kidney cells have not yet produced tumors in CBA mice. It thus appears possible to make hybrid lines from human tumor primary suspensions fused with a continuous mouse line. It is not known whether a particular hybrid is derived from tumor cells or from normal cells associated with the tumor. (3 refs.)

77-0586 **The Effects of Biotin and Fatty Acids on SV3T3 Cell Growth in the Presence of Normal Calf Serum.** (Eng.) Messmer, T. O. (Molecular Biology Lab., Salk Inst., PO Box 1809, San Diego, CA 92112) *J Cell Physiol* 90(2): 265-270; 1977.

The addition of either biotin or certain unsaturated fatty acids enhanced the growth of SV3T3 cells in medium with a low concentration (0.20% v/v of normal calf serum: 200

picrograms/ml biotin increased the final viable cell density by up to tenfold; a combination of nervonic acid, palmitoleic acid, and arachidonic acid increased the density by fivefold. The effects of biotin and the fatty acids were additive. Saturated fatty acids did not promote growth. It is suggested that the increase in final cell density in the presence of biotin is due to the reduction of cellular death; biotin did not reduce the culture doubling time when added on the day of plating or after medium depletion. (15 refs.)

- 77-0587 Serum and Hormonal Regulation of the "Resting-Proliferative" Transition in a Variant of 3T3 Mouse Cells.** (Eng.) Armelin, M. C. (Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, CP 20780, São Paulo, Brazil) *Nature* 265(5590): 148-151; 1977.

The finding of ST1, a variant of 3T3 mouse cells that is inhibited by glucocorticoids, is reported, and its value in studies of resting-proliferative transition is discussed. New cell types were sought by cloning mutagenized and nonmutagenized 3T3 populations and inspecting confluent monolayer cultures for foci of piled-up variants. Repeated plating in low serum of nonmutagenized cultures containing foci yielded a population enriched with variant cells that was then cloned and recloned. One of these clones was designated ST1. ST1 cells have diminished density inhibition of growth, serum dependence, and half as many chromosomes as the parental line, and their synthesis of DNA is inhibited by hydrocortisone. The hydrocortisone inhibition of growth has the following features: (1) it is specific for glucocorticoids; (2) glucocorticoids are effective at physiological doses; (3) it depends on serum concentration; (4) it is completely reversible and the glucocorticoids have no effect on cell viability; (5) it increases progressively with time after glucocorticoid addition; (6) glucocorticoids have no detectable effect on ongoing DNA synthesis or the ability of cells to undergo mitosis; and (7) 100% of the cells from an exponentially growing culture are found in a resting state 15-20 hr after serum step-down in the presence of hydrocortisone. It is concluded that glucocorticoids at physiological doses inhibit ST1 cell growth without compromising their viability or interfering with the biochemical processes of the S, G₂, or mitotic phases of the life cycle. The glucocorticoid seems to cause a resetting of the growth control mechanisms of ST1 cells, leading to a strict resting state with serum step-down and a large G₁ upon restimulation by serum step-up. (21 refs.)

- 77-0588 Serum Requirement and Density Dependent Inhibition of Human Malignant Glioma Cells in Culture.** (Eng.) Lindgren, A. (Wallenberg Lab., Univ. Uppsala, S-75122 Uppsala, Sweden) Westermark, B. *Exp Cell Res* 104(2): 293-299; 1977.

The glioma line U-251 MG was employed in a study of the influence of serum and cell density in relation to the impor-

tance of starvation and contact inhibition. Compared to normal glia cells (line U-787 CG), glioma cells grew to a higher terminal cell density and were less serum-dependent. A plateau phase, with retention of tumor cells in the G₁ phase of the cell cycle, was reached even under steady-state conditions. However, thymidine labeling showed noticeable cycling of cells on day 29 at all serum concentrations (2%-30%). Studies were also conducted on dense layers of cells that were wounded 3 days after a medium change. In this study a partially retained density-dependent inhibition of glioma cell growth was also demonstrated in the complete absence of serum, arguing against growth factor depletion as the sole reason for growth inhibition in crowded cultures. It is postulated that this reduced density-dependent growth inhibition of glioma cells may be due to two operationally distinct and not necessarily related malfunctions: (1) a decreased serum requirement, accounting for a capacity to grow well beyond confluency; (2) an inability to accomplish perfect physiological intercellular contact relations, which would explain the apparently unavoidable escape of a proportion of the cells into the cell cycle even at a high cell density under these conditions. (23 refs.)

- 77-0589 Serum-Free Cultivation of Thymus Organ Fragments.** (Eng.) Lub, J. R. (Biology Dept., Atlanta Univ., Atlanta, GA 30314) *Fed Proc* 35(14): 2555-2558; 1976.

To develop an in vitro model of leukemogenesis, thymic organ fragments were cultured. Thymuses were removed from 11-day-old C57BL/Ka mice and cut into 1 mm strips, which contained both cortex and medulla. The fragments were placed on filters in a culture dish with Eagle's Minimal Essential Medium with four times the usual amount of amino acids and vitamins. Cultures were performed in serum, hydrocortisone or insulin alone, or in combinations of the two hormones. Hydrocortisone and insulin alone appeared to eliminate the medulla and induced some dedifferentiation in the cortical lymphocytes. Organ fragments incubated in 10% fetal calf serum showed both a cortex and a medulla but were broken and depleted. The combination of hormones maintained a culture that most resembled the normal uncultured thymus. The organs incubated in serum sloughed more cells than those in other cultures. Cultures prepared from single cell suspensions showed some round lymphoidlike cells and some large unattached cells. It is possible that the depletion during the first wk of fragment culture represented the destruction of the short-lived lymphocytes. This depletion was followed by repopulation of the cultured organ by the long-lived hydrocortisone-resistant lymphocytes. (14 refs.)

- 77-0590 Replacement of Serum by Hemolysate as Growth Promoter for Murine Leukemic and Normal Hemopoietic Progenitor Cells in Culture.** (Eng.) Rothmann, J. (Dept. Life Sciences, Bar-Ilan Univ. Ramat-Gan, Israel) Hertogs, C. F.; Pluznik, D. H. *Exp Hematol* 5(2): 117-124; 1977.

The ability of lysates prepared from rat erythrocytes to replace serum as in vitro growth promoters for murine leukemic and normal hemopoietic progenitor cells (CFU-C) was investigated. Normal bone marrow from 6- to 10-wk-old ICR male mice and three leukemic cell lines (myeloid, P-1081; lymphoid, L-1210; and mastocytoma, P-815) were used. A total of 6×10^4 normal bone marrow or 4×10^2 leukemic cells per plate were cloned in soft agar. Addition of hemolysate to the agar medium at a final concentration of 4% promoted the growth of leukemic colonies, similar to the number of colonies obtained when 20% horse serum was added to the soft agar. Addition of 10% hemolysate or 40% horse serum promoted the growth of a comparable number of colonies of CFU-C. Rat hemolysate can therefore replace horse serum as a growth promoter of leukemic and normal CFU-C in culture. Rat hemolysate cannot, however, substitute for the colony stimulating factor (CSF) needed for the cloning of CFU-C, but addition of hemolysate, CSF, and serum to the soft agar cultures promoted a potentiated rather than an additive growth of CFU-C. (11 refs.)

77-0591 The Effect of Protein Nutrition on Host and Tumor Metabolism. (Eng.) Ota, D. M. (Dept. Surgery, Univ. Texas Medical Sch. at Houston, Houston, TX 77031) Copeland, E. M.; Strobel, H. W.; Daly, J.; Gum, E. T.; Guinn, E.; Dudrick, S. J. *J Surg Res* 22(3): 181-188; 1977.

Buffalo rats bearing Morris hepatoma 5123 were fed a regular diet ad libitum for 14 days and a protein-free diet for the next 14 days. The rats were then divided into three groups: Group I continued on the protein-free diet, Group II resumed the regular diet, and Group III received iv hyperalimentation (IVH) at 250 calories/kg/day. On day 35, the animals were sacrificed. Nutritional repletion did not produce significant changes in tumor wt:body wt ratios, although absolute tumor wt was somewhat greater in Group II and III. Hepatic fructose 1,6-diphosphatase (FDPase) activity was significantly higher in Group I rats, but GPT and GOT activities were lower. Conversely, protein repletion in Groups II and III lowered the hepatic FDPase, increased the GPT and GOT activities, and increased the liver protein levels. At the same time, tumor GPT and GOT activities were lower, but the tumor wt:body wt ratios and tumor protein levels did not increase in protein repleted rats. These data suggest that nutritional regimens such as IVH can protein-replete the malnourished host and simultaneously decrease tumor utilization of alanine and aspartic acid for energy production. (25 refs.)

77-0592 Interferon and Cell Division. XII. Prolongation by Interferon of the Intermitotic Time of Mouse Mammary Tumor Cells In Vitro. Microcinematographic Analysis. (Eng.) Collyn d'Hooghe, M. (Institut de Recherches sur le Cancer, U124 INSERM 59020 Lille Cedex, France) Brouty-Boye, D.; Malaise, E. P.; Gresser, I. *Exp Cell Res* 105(1): 73-77; 1977.

By using time-lapse photomicrography, the effect of mouse interferon on the intermitotic time of EMT6 tumor cells in monolayer cell cultures was investigated. Forty-nine cell pedigrees comprising 758 individual intermitotic times were prepared. Cultivation in the presence of interferon resulted in a marked and progressive increase in the median intermitotic time. It was observed in the first generation and it increased with each succeeding generation. The distribution of generation times, however, was not modified by interferon. Cultures without interferon (controls), those with human interferon, and those with heat-inactivated interferon did not exhibit any inhibition or antiviral activity on these cells. Almost all untreated cells underwent four successive divisions. There was no effect of interferon on the division potential of cells during the first two generations; however, a decrease in the number of dividing interferon-treated cells was observed in the third and, especially, fourth generations. The 24% of those cells that did not divide in the fourth generation could be put into three groups: cells that were damaged, cells that fused with sister cells, and cells that did not divide for a period of observation equivalent to two generation times, despite a normal appearance. The increase in tumor cell generation time may permit host mechanisms to deal more effectively with a growing tumor and, therefore, increase tumor cell destruction. (17 refs.)

77-0593 Accumulation of Polyploid Cells and G2-Phase Cells During Ascites Tumor Growth. (Eng.) Andersson, G. (Inst. Zoophysiology, Univ. Lund Helgonavagen 3b, S-223 62 Lund, Sweden) *J Cell Physiol* 90(2): 329-335; 1977.

The tumor cells employed were derived from a hyperdiploid subline of an Ehrlich ELD ascites tumor that was routinely transplanted every seventh day to 6-wk-old NMRI male mice. The tumor cells from the plateau phase of growth were transplanted into new hosts, pulse-labeled with tritiated thymidine, and blocked with repeated injections of vinblastine. The cellular DNA content of the unlabeled cells was analyzed cytophotometrically. In relation to the total number of cells (labeled plus unlabeled), 13% of the unlabeled cells had a 2C DNA content, 36% a 4C DNA content, and 5% an 8C DNA content 0.5 hr after transplantation ip inoculation of 2.8×10^6 cells. The distributions changed dramatically by 24 hr. The initially unlabeled 2C cells were now 4C, the cells that were 4C partitioned into 24% that were still 4C and 12% that progressed to 8C, and the 8C cells remained 8C. The study indicates that the accumulation of 4C cells during the plateau phase is due to a combination of G2 diploid and G1 tetraploid cells. (26 refs.)

77-0594 Mouse Teratocarcinoma. Carbon Source Utilization Patterns for Growth and In Vitro Differentiation. (Eng.) Avner, P. (Service de Genetique Cellulaire du College de France et de l'Institut Pasteur, 75015

Paris, France) Dubois, P.; Nicolas, J. F.; Jakob, H.; Gaillard, J.; Jacob, F. *Exp Cell Res* 105(1): 39-50; 1977.

Carbon source utilization patterns for both in vitro growth and differentiation of the embryonal carcinoma line PCC3/A/1 were studied. Of the carbon source substrates tested, only glucose and mannose were capable of supporting the habitual complete terminal differentiation sequence. In the absence of glucose, differentiation is apparently blocked during the second part of the differentiation period. By altering the carbon source, cell variants of PCC3/A/1 were isolated, and the results of a preliminary characterization of these cell lines are discussed. (22 refs.)

77-0595 Demonstration of Considerable Amounts of Glycogen or a Similar Substance in Embryonal Cells and in Human Colon Carcinomas by Rabbit Antisera to *Escherichia coli* 013. (Fre.) Zweibaum, A. (Institut d'Immunologie, I.N.S.E.R.M. U 120, Hopital Broussais, 96, rue Didot, 75674 Paris Cedex 14, France) Rousset, M.; Leon, S.; Martin, F.; Burtin, P. *C R Acad Sci D (Paris)* 284(1): 105-108; 1977.

Rabbit antisera to *Escherichia coli* 013, with strong antiglycogen activity, were tested on normal human fetal and adult colons, on colon carcinomas, and on cultured colon tumor cells (HT29). The immunofluorescence test revealed only very rare granules in normal adult colon. In fetal colons, in 12/14 carcinomas, and on HT29 cells, the immunofluorescence reactions were similar to those observed in normal liver. The reaction was negative after pretreatment with α -amylase. The reaction was inhibited by glycogen, phenol-alcohol, perchloric and trichloroacetic acid extracts from fetal colons, and by a tumor trichloroacetic acid extract. The extracts precipitated with anti-*E. coli* 013 antisera. They had strong inhibiting activity in a radioimmunoassay with labeled glycogen. The extracts from normal adult colons did not precipitate with the antisera, and they had no inhibiting activity in either immunofluorescence tests or radioimmunoassays. Further studies will be necessary to determine whether the glycogen or glycogenlike substance found is colon specific or whether it occurs in other organs as well. (12 refs.)

77-0596 Growth Characteristics and Tumorigenicity of Long-Term Cultures of the Rat RBA Myelogenous Leukemia. (Eng.) Svec, J. (Cancer Res. Inst., 880 32 Bratislava, Czechoslovakia) Hlavayova, E.; Thurzo, V. *Neoplasma* 23(6): 609-616; 1976.

The tumorigenicity and growth characteristics of long-term cultures of the rat RBA myelogenous leukemia were assessed. Velocity sedimentation of RBA-RC cells in a gravitational field resulted in three peaks of light absorbance, as measured at 600 nanometers. Peak 1 demonstrated the presence of small rounded cells with pycnotic nuclei. Another small peak of light absorbance did not contain visible cells but did con-

tain an excess of cellular debris. None of these two peaks contained material that incorporated ^3H -thymidine. The main peak showed the presence of myeloblasts, which were homogenous in size and incorporated ^3H -thymidine. These cells (RBA-BC) were collected by centrifugation, washed in phosphate-buffered saline, and recultured. The generation time and the value of the S phase of these cells were compared with those of XC cells. The rate of incorporation of ^3H -thymidine, as determined radioautographically in the RBA-BCv metaphase cells, reached maxima faster than in the XC cells. The difference in generation times and synthetic phase values between RBA-BCv and XC cells correlated with the different doubling times of each cell line. The banding karyotype analysis revealed that the RBA-BCv cells possessed a karyotype with a modal number of 41-42 chromosomes. The stemline karyotype contained two larger metacentric markers and one large subtelocentric chromosome marker. The RBA-BCv cells were negative for myeloperoxidase as well as with Sudan Black B and PAS stainings. Only a slight difference in tumorigenicity for adult rats was noted between in vivo and in vitro cells. RBA leukemia cells kept in vivo, after transplantation of as few as 10 cells per animal, produced leukemia in 100% of the animals, with a 23-day av survival time. The same incidence could be obtained with an inoculum of 1,000 RBA-BC cells per animal. In comparison to the parental RBA-BC cell line, the tumorigenicity of the RBA-BCv cells seems to be slightly higher. (20 refs.)

77-0597 Effects of Some Low Molecular Weight Sheep Pineal Fractions and Melatonin on Different Tumors in Rats and Mice. (Eng.) Lapin, V. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 81, A-1090 Vienna IX, Austria) *Oncology* 33(3): 110-113; 1976.

The influence of low-molecular-wt sheep pineal fractions and melatonin on tumors in mice and rats was studied. The separation of aqueous sheep pineal and sheep cerebral cortex extracts on Sephadex G-25 produced several distinct peaks showing excitation and fluorescence maxima resembling those of indoles. The fractions of a 100-g extract of sheep pineals were scanned and compared with similar fractions obtained from 100 g of sheep cerebral cortex. A high peak demonstrating an excitation max of 305-310 nanometers and a fluorescence max of 350-355 nanometers was obtained in the pineal extract. This fraction (F3) was very active in inhibiting compensatory ovarian hypertrophy. A slight inhibitory activity was found in another fraction (F2). Fractions F2 and F3 were combined and separated by ultrafiltration. The effects of the resulting fractions (UM-2R and UM-O5R) on tumor-bearing animals were evaluated. In contrast to UM-2R, injections of UM-O5R increased the survival time of intact female Wistar rats bearing Yoshida sarcoma. When the influence of pineal fraction UM-O5F Sephadex G-10 fraction F3 and melatonin on Lewis lung carcinoma in DBF1 male mice was tested, melatonin was found to reduce survival time, but the pineal fraction prolonged it. The effect of pineal fraction UM-2R and melatonin on methylcholanthrene (MCA)-induced tumors in the mice was also studied. Tumor appear-

ence was delayed in mice treated by melatonin. However, 17 wk after the first injection of MCA and 10 wk after the last treatment dose, only one animal treated with UM-2R developed a tumor; at the same time, in the group injected with melatonin, 8 animals already had tumors, but in the group injected with saline only, 16/30 had tumors. (25 refs.)

77-0598 Delayed Malignancy and Altered Growth Properties of Somatic Cell Hybrids Between Rat Hepatoma and Mouse L-Cells. (Eng.) Lyons, L. B. (Lab. Biochemistry, NCI, NIH, Bethesda, MD 20014) *J Cell Physiol* 130(2): 179-191; 1977.

A study was made of the in vitro growth properties and in vivo tumorigenic potential of three hybrid clones derived from the fusion of rat hepatoma HTC-H1 cells with mouse L-B82 cells. One hybrid clone, 07, had a very flat morphology, was subject to density-dependent inhibition of growth (DDIG), and had a relatively low saturation density. Clone V4a had a flat morphology, was not sensitive to DDIG, and had a high saturation density. Clone V5 had an atypical morphology, having elongated overlapping processes, was not subject to DDIG, and possessed a relatively high saturation density. All three hybrid cell lines produced tumors in nude mice a good deal later than did the parent cell lines at identical injection doses (10^5 - 10^6 cells). The L cells gave rise to fibrosarcomas, and the HTC cells produced typical hepatomas; all the hybrid clones gave rise to fibrosarcomas and, in some instances, to less well-differentiated tumors. Consistent with the delayed appearance of the tumors in vivo, all of the hybrid clones produced colonies suspended in agarose gels that were much smaller than those produced by the parent cell lines in the same period of time. The mean chromosome numbers of each of the cell lines were 50, 110, 133, 95, and 98 for the L, HTC, 07, V4a, and V5 cells, respectively; these chromosome numbers remained unchanged after growth in agarose gel or as tumors in nude mice. (23 refs.)

77-0599 Teratocarcinoma \times Friend Erythroleukemia Cell Hybrids Resemble Their Pluripotent Embryonal Carcinoma Parent. (Eng.) Miller, R. A. (Dept. Human Genetics, 1044 Kline Biology Tower, Yale Univ., New Haven, CT 06520) Ruddle, F. H. *Dev Biol* 56(1): 157-173; 1977.

Five monolayer cell lines were derived from two fusion experiments between cells of the pluripotent teratocarcinoma-derived embryonal carcinoma line PCC4azal and FBU Friend erythroblastic leukemia cells. All five lines closely resembled their PCC4azal parent. They resembled embryonal carcinoma cells by phase contrast and electron microscopy, had high levels of alkaline phosphatase but low levels of acetylcholinesterase activity, and, like PCC4azal, expressed lactate dehydrogenase-A (LDH-A) and LDH-B. Tumors from these hybrid lines often contained large amounts of differentiated tissue, which included elements of all three germ layers. Tumors with the greatest variety of tissue types also contained the largest proportion of non-embryonal carcinoma cells. These results indicate that the genome of a pluripotent mammalian cell may be able to "reset" the genome of a differentiated cell. (50 refs.)

77-0600 Spontaneous Malignant Transformation in Two Epithelial Cell Lines of Rat Liver Cells. (Eng.) Masuji, H. (Div. Pathology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan) *Acta Med Okayama* 30(5): 359-370; 1976.

Experiments were conducted to determine whether B and J-13 cells could undergo spontaneous neoplastic transformation during in vitro serial cultivation and to determine the nature of the tumors produced by inoculation into Donryu rats. Cells of the B line produced hemorrhagic ascites tumors in rats after 80 subcultures (approx 10^7 cells inoculum). The mean latency period after inoculation was 384 days; the percentage of takes was 46.4%. With line J-13, cells inoculated (approx 10^7 cell inoculum) after subculture 58 produced tumors with a mean latent period of 251 days. The percentage of takes was 50%. The tumors generally killed the animals within 2 wk of abdominal enlargement. There were large numbers of nodules in the omentum, and metastases were observed in the peritoneum, diaphragm, lungs and liver. The cells maintained normal diploidy until about the day 300 (30 subcultures); at about day 600 to 700, hypotriploid cells became predominant. With increasing time in culture, the cells showed a heterogeneous morphology; the growth rate also increased with cultivation. The detailed mechanism of spontaneous malignant transformation in vitro is unknown. (12 refs.)

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μ l	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μ Ci	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μ g	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intradermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μ M	micromolar		

REVIEW

7-0601 **The Utility of Short-Term Tests for Mutagenicity as Predictive Tests for Carcinogenic Activity.** (Eng.) De Serres, F. J. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. New York: American Elsevier Publishing Co., Inc.): Vol. 17, p. 113-117; 1976.

Brief discussion is made of the efficacy and utility of short-term microbial tests for detecting mutagens/carcinogens. A series of three workshops on the subject (held at Brussels, Tokyo, and Honolulu) has resulted in the following conclusions. (1) The best correlation between mutagenicity and carcinogenicity was obtained with microbial assay systems for mutation induction or DNA repair in *Salmonella typhimurium*, *Escherichia coli*, and *Bacillus subtilis* in combination with tests for in vitro metabolic activation. (2) At least 80% of chemical carcinogens are mutagenic, and < 10% of presumed noncarcinogens gave false-positive results. When noncarcinogenic chemicals were selected at random (ie, without the deliberate inclusion of structural analogs of known carcinogens) only 1%-2% were positive. (3) The tests have immediate utility and great future potential for the screening of industrial/environmental materials. (4) In order to eliminate false negatives (carcinogens not detected by the short-term tests), greater priority should be given to the development of assays for forward mutation, which will detect any type of genetic alteration, rather than reverse mutation, which only detects particular types of genetic alterations. (2 refs.)

7-0602 **Flame-Resistant Additives as Possible Cancer Hazards.** (Eng.) Blum, A. (Biochemistry Dept., Univ. California Berkeley, Berkeley, CA 94720) *Science* 195: 7-23; 1977.

Flame-retardant additives as possible cancer hazards are discussed. Tris-(2,3-dibromopropyl)phosphate (tris-BP), the main flame retardant currently used in children's pajamas, is a mutagen. For man-made fibers, tris-BP is by far the most important flame-retardant compound in use, and perhaps 10 million pounds per yr are utilized in fabrics and plastics. It is almost exclusively used in polyester, acetate, and triacetate fibers, as well as being the basis for a successful finish to acrylic carpets. The utilization of tris-BP is currently the most economical, convenient way to meet the children's sleepwear standards. The possible consequences of the widespread use of tris-BP are serious. It does come off fabric, is at least topically absorbed, is known to be a strong mutagen,

and may contain a potent carcinogen as an impurity. The tris-BP made by Michigan Chemical and utilized for textiles contains 0.05% of the impurity 1,2-dibromo-3-chloropropane. Dibromochloropropane causes a high incidence of squamous carcinoma of the stomach in both rats and mice as early as 10 wk after initiation of feeding. In addition, 50% of the female rats develop mammary adenocarcinomas. Infants' and young children's habit of sucking their clothing can lead to its ingestion. In addition to the hazard posed by tris-BP to those who make, work with, and wear fabrics treated with it, an environmental hazard may be posed by its disposal in large quantities into water and soil. The simulated washing of six treated sheets in a total vol of 30 gallons of water yields approx 6 ppm of tris-BP in the wash water. A concentration of 1 ppm in water is sufficient to kill goldfish within 5 days. At present, no government agency has the authority for ensuring long-term safety of textile additives such as flame retardants, although the toxic substances law might eventually solve this problem. (66 refs.)

77-0603 **Asbestos.** (Eng.) IARC Working Group. In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man.* International Agency for Research on Cancer. (Lyon, France): Vol. 14, pp. 2-106; 1977.

An evaluation of the carcinogenic risk of asbestos, based on all available data published or accepted for publication up to December 1976, is presented. The six fibrous silicates of asbestos considered are serpentine chrysotile (CH) and amphiboles actinolite, amosite (AS), anthophyllite (ATH), crocidolite (CR) and tremolite. Three subjects are discussed: (1) chemical and physical data; (2) production, use, occurrence and detection of asbestos, and (3) biological data relevant to the evaluation of carcinogenic risk to man. All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters and rabbits. Fibers less than 0.5 μ m in diameter are more active in producing tumors than larger fibers. Glass fibers and nemalite of this size can also produce mesotheliomas. In humans a high incidence of lung cancer follows occupational exposure to CH, AS, ATH or mixed fibers containing CR. Many pleural and peritoneal mesotheliomas have been observed after occupational exposure to CR, AS and CH. An excess risk of gastrointestinal tract and larynx cancers has followed exposures to AS, CH or mixed fibers containing CR. Mesotheliomas occur in individuals living near asbestos factories and CR mines and in household contacts of asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibers independently increase lung cancer incidence, but when present together they act synergistically. (286 refs.)

- 77-0604 **Aflatoxins and Their Relation to Hepatocellular Carcinoma.** (Eng.) Wogan, G. N. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 25-41; 1976.

Chemically, aflatoxins are highly substituted coumarins that contain a fused dihydrofurofuran configuration peculiar to a limited number of compounds of natural origin. Aflatoxins have carcinogenic activity in many species of animals, including rodents, nonhuman primates, birds, and fish. The liver, in which the toxins induce hepatocellular carcinomas and other tumors, is the organ principally affected. Considerable research is being done on the metabolism of aflatoxin B₁ to determine its mode of action and the differences in susceptibility among various animal species. The epoxidation pathway may represent a significant activation step in aflatoxin metabolism. Aflatoxins provide structural homologs for investigations of relationships between chemical structure and biological activity. They are among the few chemically identified and widely disseminated environmental carcinogens for which quantitative estimates of human exposure have been sought systematically. The risk of exposure is evidently much less in technologically developed countries than in developing areas. Although the absolute values of aflatoxin ingestion appear small quantitatively, their potency as carcinogens in animals must be kept in mind in order to put data into perspective. (58 refs.)

- 77-0605 **On the Pathogenesis of Experimental Hepatocellular Carcinoma.** (Eng.) Farber, E. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 3-22; 1976.

The pathogenesis of experimental hepatocellular carcinoma is examined. The compounds currently considered the most significant in relation to human liver cancer are the mycotoxins, especially the aflatoxins. Most hepatocarcinogens are not carcinogens per se, but are metabolically converted to highly reactive derivatives. These activated electrophiles undergo a variety of reactions with components in nucleic acids, proteins, and probably many other cellular constituents. Biologically, the initiation of hepatocellular carcinoma seems to consist of the induction of a new hepatocyte population that differs in several respects from the original. It is more resistant to the cytotoxic environment created by the carcinogenic process, which allows it to proliferate. It also contains an antigen so far not found in normal liver, and it proliferates in patterns resembling fetal and neonatal liver. Early in the development of liver cancer, the carcinogen induces a new cell population that appears as multiple scattered foci, creates an appropriate selection pressure, and interrupts differentiation or remodeling. The phenomenon of arrested differentiation or aborted development may be an important principle in the pathogenesis of hepatocellular carcinoma. Both somatic mutation and altered differentiation may each play a significant role at different stages of the process. There appears to be a continual selection of smaller and smaller numbers

of cells, each with an increasingly greater probability of development of cancer. (123 refs.)

- 77-0606 **Benzo(a)pyrene Metabolism: Enzymatic and Liquid Chromatographic Analysis and Application to Human Tissues.** (Eng.) Gelboin, H. V.; Okuda, T.; Selkirk, J. K.; Nemoto, N.; Yang, S. K.; Rapp, H. J.; Bast, R. C. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magie, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: University Park Press): pp. 167-190; 1976.

The characteristics and estimation of aryl hydrocarbon hydroxylase, benzo(a)pyrene-4,5-oxide hydratase, and glutathione S-benzo(a)pyrene-4,5-oxide transferase in human monocytes, lymphocytes, and liver and in rat liver are discussed. The products of benzo(a)pyrene (BP) metabolism in these tissues were analyzed by high-pressure liquid chromatography (HPLC). The human tissues formed five new unidentified metabolites not previously seen in rat experiments. In addition, the predominant form of the diol epoxide of BP made by rat liver microsomes is the r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene derivative, which has a much greater mutagenic activity than any known BP metabolite. (65 refs.)

- 77-0607 **Cancer and Carcinogenesis.** (Eng.) Ball, C. R.; Clayson, D. B. In: *The Cell in Medical Science*. Beck, F.; Lloyd, J. B., eds. (New York: Academic Press): Vol. 4, pp. 357-404; 1976.

Cancer is a disease of multicellular organisms. It is believed to be the clinical manifestation of usually irreversible failure in the biological and biochemical mechanisms that maintain the integrity and relative size of tissue in the organism. Tumors can be induced easily in experimental animals, but it is difficult to develop methods to study the mechanisms of carcinogenesis. Slight variations in the experimental conditions may have an effect on tumor yield. Evidence that chemicals, viruses, and radiation can modify genetic material is summarized. In a unifying theory of carcinogenesis, the initial event can be regarded as a somatic cell mutation. This and other theories are discussed. Chemical carcinogens are not always industrial or synthetic substances; some of the most potent agents, such as the mold metabolite aflatoxin, are of natural origin. The great diversity in the chemical structure of carcinogens suggests a multiplicity of mechanisms for the chemical induction of cancer. Radiation induces damage in biological material as a result of the energy transferred to that material in decelerating a high-energy particle or in absorbing the electromagnetic radiations. The energy transferred is sufficiently high to cause the rupture of chemical bonds. Viruses act by imparting new information

in the genome. The nature of the critical changes in the genome is still a matter of speculation. In cancer, the homeostatic mechanisms that maintain the integrity of the normal organism are lost. (90 refs.)

77-0608 The Role of the Liver in Chemical Carcinogenesis. (Eng.) Magee, P. N. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London, WIPR, United Kingdom) *Panminerva Med* 18(11/12): 427-32; 1976.

The role of the liver in chemical carcinogenesis is assessed. The balance of the available evidence indicates that nitroso compounds act after conversion in the body into alkylating intermediates, possibly carbonium ions, which react with nucleophilic centers in the nucleic acids, proteins and other cellular components. The nitrosamines appear to be activated by enzymes of the microsomal hydroxylase type, while the nitrosamides yield carcinogenically active products without the necessity of enzyme action. The rat liver is apparently resistant to single doses of nitroso carcinogens. Measurable methylation and quite substantial ethylation may occur on the O⁶-position of guanine in nucleic acids of animals treated with alkylating agents. The persistence of O⁶-ethylguanine has been compared in brain and liver of 10-day-old rats treated with single doses of N-ethylnitrosourea under conditions known to induce tumors selectively in the brain but not in the liver. Similar initial degrees of ethylation have been found in the DNA of both organs in terms of molar fractions of O⁶-ethylguanine, 7-ethylguanine, and 3-ethylguanine at 1 hr after the injection of the carcinogen. However, the rate of removal of O⁶-ethylguanine over a 240 hr period after the injection is significantly slower in brain than in liver and also much slower than the elimination rates from brain of 7-ethylguanine and of 3-ethyladenine. If alkylation of guanine on the O⁶-position of DNA is related to the induction of cancer, as data suggest, an explanation for the resistance of the liver to carcinogenesis is provided by the much greater capacity of this organ to remove the anomalous base from its DNA. The liver can remove potentially mutagenic O⁶-alkylguanines from its DNA. (49 refs.)

77-0609 Chemical Carcinogenesis: Bioactivation and Biochemical Lesions. (Eng.) Neumann, H. G. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. XVII, pp. 13-20; 1976.

The dose-effect relationships in chemical carcinogenesis are discussed. Because there are competing pathways for the activation and deactivation of drugs, effective levels of toxic/carcinogenic metabolites may be changed by influences other

than dose-dependent drug concentrations. For example, the binding of acetaminophen (AP) metabolites to liver macromolecules, which correlates to the severity of AP-induced liver necrosis, remained very low up to a certain AP dose and then increased proportionally with the dose above this threshold. This threshold effect was found to be caused by the depletion of intracellular glutathione concentrations, resulting in glutathione becoming rate-limiting for the detoxifying conjugation reaction of the AP metabolites. Also, the total binding of carcinogen-derived metabolites to cellular components cannot be correlated unequivocally with biochemical lesions. The total binding of trans-4-dimethylaminostilbene (DMAS) metabolites to rat liver constituents (17.4 nanoM/g liver) was found to be much higher than the binding to constituents of Zymbal's gland (2 nanoM/g) 24 hr after the administration of 1 mg/200 g of DMAS, although DMAS induced tumors in Zymbal's gland but not in the liver. The pattern of metabolism of some materials is known to be dose-dependent: at low doses (0.1 mg/200 g rat) of diethylstilbestrol (DES), glutathione-conjugated biliary DES metabolites were predominantly nonpolar; however, they were predominantly polar when high levels (10 mg/rat) of DES were administered. (18 refs.)

77-0610 Chemical Carcinogenesis: Early Morphological and Cytochemical Changes. (Eng.) Bannasch, P. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. 17, pp. 21-23; 1976.

A review is presented of electron microscopic and cytochemical studies of early lesions found in the livers and kidneys of rats intoxicated by nitrosomorpholine or thioacetamide. Liver cells display many different reactions to the influence of hepatocarcinogens. (1) Reversible alterations, which result from nonspecific toxic effects and parenchymal regeneration, such as centrilobular glycogen loss, disorganization of the rough endoplasmic reticulum (ER), toxic necrosis, increase in mitotic rate, diverse mitotic abnormalities, and megalocytosis, are one type. These changes disappear within 2-4 wk of cessation of treatment, regardless of the dosage applied. (2) Persistent cytoplasmic alterations are observed in hepatocytes believed to be precursors of neoplastic cells. These alterations include an excessive storage of glycogen and hypertrophy of the smooth ER. (3) Progressive changes, which occur not only during treatment, but also after withdrawal of the carcinogen, include gradual reduction of excess stored glycogen and an increase in cytoplasmic basophilia. Three distinct stages of multicystic cholangioma formation in the livers of nitrosomorpholine (or other carcinogen)-treated rats are observed. The first stage involves vigorous proliferation of bile duct epithelia and mesenchymal cells, with subsequent fibrosis. The second stage involves a conversion of initially oval epithelia to cylindrical cells that secrete abundant mucopolysaccharides. In the third stage, the mucous cholangiofibrosis often gives rise to multicystic cholan-

giomas. The development of most epithelial liver and kidney tumors is linked with the pathological storage of polysaccharides or lipids. (29 refs.)

- 77-0611 Chemical Carcinogenesis: Early Biological Responses in Induced Carcinogenesis of the Kidney.** (Eng.) Butler, W. H.; Hard, G. C. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. 17, pp. 34-38; 1976.

Description is made of the morphological and histochemical features of premalignant kidney tissues after treatment of rats with an LD₅₀ dose of dimethylnitrosamine (DMN) and of similarly premalignant livers during and after the feeding of rats with a diet containing 5 ppm of aflatoxin for 6 wk. In both instances, there is a continuous sequence of events leading from acute toxic injury to a chronic reaction that results in recognizable neoplasia. Following DMN treatment, an acute phase of about 2 wk is observed: after 24 hr, interstitial fibroblasts of the kidney cortex have autophagic vacuoles and other cytoplasmic abnormalities; a wave of proliferation of interstitial fibroblasts peaks after 6 days; and a peak inflammatory reaction occurs around the seventh day as a result of the necrosis of a few scattered proximal tubule cells. Persistent hypocellular foci, with abundant plasma cells, lymphocytes, and macrophages, are observed during a chronic reaction phase lasting from about 2 to 12 wk after treatment. After 12 wk, there is a rapid proliferation of mesenchymal foci that leads to unequivocal microscopic neoplasms after 20 wk. These observations suggest that the neoplasm is induced as an acute phenomenon, the cell of origin being an interstitial cortical fibroblast or, possibly, an extramural pericyte that retains its vasoformative properties. (13 refs.)

- 77-0612 Covalent Binding and Endogenous Incorporation as Illustrated by Nitroso Carcinogens.** (Eng.) Magee, P. N. (Fels Res. Inst., Temple Univ. Sch. Medicine, 3420 N. Broad St., Philadelphia, PA 19140) *J Toxicol Environ Health* 2(4): 883-893; 1977.

The results of metabolic experiments using radioactively labeled drugs or other foreign chemicals are interpreted in terms of safety evaluation. The carcinogenic potential is different if the radioactivity represents covalent binding to a cellular macromolecule, as opposed to incorporation via normal metabolic pathways of decomposition products. These two types of binding are illustrated by carcinogenic nitroso compounds such as dimethylnitrosamine and N-methylnitrosourea. Dimethylnitrosamine requires metabolic activation by microsomal enzymes to yield a chemically reactive methylating intermediate. N-Methylnitrosourea yields the same methylating intermediate spontaneously, under

physiologic conditions, and causes covalent binding in the body. There is little direct evidence on the carcinogenicity of food containing covalently bound residues of chemical carcinogens. The possibility of incorporation of radioactivity via normal metabolic pools must always be considered when the nature of persistent radioactivity is investigated in animals treated with radioactive chemicals. It is unlikely that food containing covalently bound residues is carcinogenic, unless the residue is further metabolized to form another ultimate carcinogen. (38 refs.)

- 77-0613 Early Cell Changes in the Course of Chemical Carcinogenesis.** (Eng.) Butler, W. H. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975.* Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 89-102; 1976.

The structural and biochemical properties of cells undergoing chemically induced neoplastic changes are reviewed. The sequential effect of an LD₅₀ dose of dimethylnitrosamine (DMN) on renal epithelial and mesenchymal cells in survivors was studied. Unequivocal evidence of autonomous growth and invasion required about 20 wk. Continuous cultures of kidney cells obtained 20 hr after in vivo treatment with DMN exhibited properties similar to those of transformed cells. Thus, neoplasia can be induced as an acute response and only time is required for a full demonstration of autonomous growth, invasion, and metastases in the host. Examination of the liver of inbred male Fischer rats fed 5 ppm aflatoxin for 6 wk revealed foci composed of either small basophilic or large eosinophilic parenchymal cells. Some basophilic foci contained starvation-resistant glycogen and/or a reduced amount of glucose-6-phosphatase; both foci showed a reduction of succinic dehydrogenase and aniline hydroxylase and a patchy loss of membrane ATPase. During the 6-wk feeding period, normal maturation to tetraploid parenchymal cells was reduced, resulting in a shift to a diploid population that persisted for the life of the animal. A major problem in interpreting these findings is which, if any, of the observed foci represent developing neoplasia and which represent a toxic response. (12 refs.)

- 77-0614 How Nitrosamines Cause Cancer.** (Eng.) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD) *New Sci* 73(1036): 216-217; 1977.

More than 120 N-nitroso compounds have been tested for carcinogenicity in animals, mostly rodents, and approx 80% of them have induced tumors. Which organs develop tumors depends to some extent on the dose administered, but the site is frequently independent of the route of administration, implying that the compounds act systemically and become easily

distributed in the body. When all the hydrogen atoms in methylnitrosamine are replaced by deuterium, fewer liver tumors are induced and they take longer to develop. Since deuterium is bound more tightly to carbon than is hydrogen, requires more energy to remove the deuterium and, therefore, fewer molecules of the deuterium-containing compound are activated. The effect of deuterium substitution on the carcinogenicity of nitrosomorpholine is similar and even more pronounced. The significance of the α -hydrogens is demonstrated by the effect of replacing one or more of them with methyl group; for example, in nitrosopiperidine. One methyl group, as in 2-methylnitrosopiperidine, reduces the carcinogenic potency by approx half, but replacement of a hydrogen on either side of the nitroso group by methyl, as in 6-dimethylnitrosopiperidine, abolishes the carcinogenic activity. A methyl group in the 3-position has almost no effect. At the 4-position, potency increases slightly. On the other hand, methyl substitution at positions other than α in some nitrosamines enormously increases carcinogenic potency. By systematically modifying the molecular structure of nitrosamines, it is proving possible to pin down their cancer-reducing activity. (no refs.)

77-0615 **Metabolism of N-Nitroso Compounds Inducing Pancreatic Cancer (Meeting Abstract).** (Eng.) Kingell, R. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Centre, Omaha, NB 68105) Kupper, R.; Wallcave, L.; Pour, P. *Xenobiotica* 7(1-2): 98-99; 1977.

In studies with Syrian hamsters, three compounds, N-nitroso-bis(2-hydroxypropyl)amine (BHP), N-nitroso-bis(2-methoxypropyl)amine (BAP), and N-nitroso-bis(2-oxopropyl)amine (BOP), have exhibited potent carcinogenic effects on the pancreas and other organs. The major urinary metabolite of both BAP and BOP was BHP. BOP showed greater specificity for the pancreas than BHP. In vivo, BOP was rapidly converted to the metabolite N-nitroso-(2-hydroxypropyl)(2-oxopropyl)amine (HPOP), which was slowly metabolized to BHP. HPOP may be a proximate pancreatic carcinogenic metabolite when BOP or BHP are administered and thus may be used in the development of an animal model for pancreatic cancer. BOP and BHP may act preferentially on the pancreas, because HPOP can exist in a cyclic form analogous to the pyranose form of glucose. (3 refs.)

77-0616 **Acridflavinium Chloride.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 31-37; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are given for acridflavinium chloride.

The compound is a mixture of acridflavine (3,6-diamino-10-methylacridinium chloride) and proflavine (3,6-acridinediamine), and is used as a topical or urinary antiseptic. Acridflavinium chloride interacts with DNA in HeLa cells, simian virus 40-transformed mouse cells, and in cultured human fibroblasts and buccal cells. It induces point mutations in *Escherichia coli*, frameshift mutations in *Salmonella typhimurium* strain his-C3076 without metabolic activation and in strains TA98 and TA1537 with metabolic activation, and respiratory-deficient petite mutants in *Saccharomyces cerevisiae*. Chromosomal abnormalities in HeLa cells and cultured peripheral human WBC were reported at concentrations of 10^{-6} M in the absence of light and at 10^{-9} - 10^{-7} M after exposure to light for 1 hr. In view of its mutagenicity, further testing of the compound for carcinogenic properties is recommended. (27 refs.)

77-0617 **8-Hydroxyquinoline.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 101-112; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are reported for 8-hydroxyquinoline (HQ), which is used as an antimicrobial drug for the treatment of minor burns and hemorrhoids and as a bacteriostatic additive in hairdressing preparations. HQ, at a dose of 20-40 μ g/plate, caused point mutations in *Salmonella typhimurium* strain TA100 in the presence of a rat liver homogenate. The sc, oral, and topical application LD50's are 7.5, 7.5, and 6 mg/animal, respectively, in mice; the sc and oral LD50's are 500 and 75 mg in rats. A number of studies in mice and rats of the carcinogenic effects of oral, sc and topical administration of HQ gave positive and negative results of only borderline significance. Positive results were obtained in bladder implantation experiments when HQ was incorporated in cholesterol pellets: 5/13 mice treated with a 9- to 11-mg cholesterol pellet containing 20% HQ developed bladder tumors, compared to 1/21 controls. HQ implantation did not cause tumors when paraffin wax pellets were used. No data concerning the carcinogenicity of HQ in man are available. (35 refs.)

77-0618 **Misrepair Model for Mutagenesis and Carcinogenesis.** (Eng.) Kondo, S. In: *Fundamentals in Cancer Prevention: Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975.* Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: University Park Press): pp. 417-429; 1976.

Studies on the molecular mechanism of carcinogenesis in relation to DNA repair, and evidence supporting the mutation

theory of transformation are reviewed. Treatment of *Escherichia coli* with the UV mimetic, oncogenic chemical 4-nitroquinoline 1-oxide (4NQO) produces 4NQO-purine adducts, which undergo excision repair without errors detectable by mutation or transformation tests. Results obtained with transformed BALB/3T3 mouse cells support the hypothesis that unexcised 4NQO-purine adducts are the major cause of transformation. Caffeine, administered after 4NQO, suppressed error-free repair at low doses and error-prone repair at high doses in *E. coli* but suppresses only error-prone repair in mouse cells, resulting in decreased transformation. Pretransformational damage is fixed (eg, unchanged by caffeine) within the first post-4NQO cell division. The 4NQO-induced transformation in mouse cells takes four generations for full expression; this result is similar to the delayed appearance of recessive membrane-mutations in *E. coli*. Results suggest that fixation of 4NQO-induced pretransformational damage occurs through a mechanism similar to that of 4NQO-induced mutagenesis in *E. coli*: errors in postreplication repair of daughter DNA defects are produced by inhibition of replication opposite 4NQO-purine adducts on old DNA template strands. Data on the relationship between radiation and leukemia in atomic bomb survivors also suggest that deletion mutations may lead to leukemia. DNA repair may be involved in the suppression of cancer in some experimental animals and may be significant in the prevention of human cancer. (30 refs.)

77-0619 Dithranol. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 75-82; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are reported for dithranol (DT: 1,8,9-anthracenetriol), which is used for the treatment of psoriasis and chronic dermatoses. DT is a tumor-promoting agent in mouse skin following initiation with either 7,12-dimethylbenz(a)anthracene (DMBA) or urethane. For example, 18/20 7-wk-old female ICR/Ha mice painted with a single application of 20 µg of DMBA in 0.1 ml of acetone, followed 2 wk later by repeated paintings (3×/wk for 490 days) with 0.1 ml of a 0.08% solution of DT in acetone, developed 94 skin tumors. Most of the tumors were papillomas, but 9 were squamous-cell carcinomas. No tumors were found in DMBA-painted rats treated at intervals with acetone alone. An increased incidence of lymphomas was also observed in mice painted with DT after urethane initiation: 21/40 ICR mice treated with 50 mg of urethane developed lymphomas after topical application of 0.033% DT in acetone, compared to only 3/40 mice treated with urethane alone. DT forms molecular complexes with calf thymus DNA in vitro and induces petite mutations in *Saccharomyces cerevisiae*. No data concerning the carcinogenicity of DT in man are available. (27 refs.)

77-0620 Ethionamide. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 83-89; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data for ethionamide (ET: 2-ethyl-4-pyridinecarbothioamide), which is used for the treatment of tuberculosis, are given. ET is carcinogenic in mice after oral administration: 7/33 female BALB/c/Cb/Se mice given daily intragastric instillations of 0.1 ml of a 2% solution of ET in propylene glycol 6 days/wk for 50 wk developed thyroid tumors (5 papillary and 2 epidermoid carcinomas) between 28-69 wk. No untreated mice developed thyroid tumors. The carcinogenicity of ET has not been tested in any other species. The ip LD50 of ET in mice is 1,350 mg/kg. In man, toxic hepatitis has been associated with the use of ET. (28 refs.)

77-0621 Metronidazole. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 113-122; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are given for metronidazole (MN: 2-methyl-5-nitro-1H-imidazole-1-ethanol), which is used to treat infections due to *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia*. It has also been used in Vincent's infection. MN is carcinogenic in mice after oral administration: eg, the incidence of lung tumors rose from 19% in untreated male Swiss mice to 77% in males given a diet containing 0.5% MN for their lifetime, and it rose from 20% in untreated females to 44% in similarly treated females. Treated female mice also demonstrated a significantly increased incidence of lymphomas. The oral administration of MN to rats increased the incidence and multiplicity of mammary fibroadenomas. No data are available as to the carcinogenicity of MN in man. In human patients receiving 750 mg/day of MN, mutagenic activity was found in the urine using *Salmonella typhimurium* as a genetic indicator. A two- to fourfold increase in the occurrence of chromosomal abnormalities was observed in cultured peripheral WBC from patients with Crohn's disease being treated with 200-1,200 mg/day of MN for 1-24 mo. (42 refs.)

77-0622 Niridazole. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 123-130; 1977.

chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data for niridazole (ND: 1-(5-nitro-2-methyl-2-imidazolidinone), which is used as a schistosomicide, are presented. ND is carcinogenic in mice and hamsters by oral administration. In Swiss mice fed a diet containing 0.05% ND, there were significantly elevated incidences of lung adenoma (37%-87% vs 4%-28% in untreated controls) and of the number of adenomas per lung-tumoring mouse (3-5 vs 1); carcinomas and papillomas of the stomach (26%-63% vs 4%); mammary carcinomas (10%-20% vs 4%); and ovarian granulosa cell tumors (7%-10% vs 0%). Transitional cell carcinomas and lymphomas were also observed. In Syrian golden hamsters fed a diet of 0.04%-0.24% ND, significant increases in the incidence of stomach tumors (15%-90% vs 0%-3% in untreated animals) and of transitional cell papillomas of the bladder were observed. Infection of the treated mice or hamsters with *Schistosoma mansoni* cercariae did not affect the carcinogenicity of the compound. No data concerning the carcinogenicity of ND in man are available. (27 refs.)

77-0623 **Phenacetin.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 141-155; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data for phenacetin [PA: N-(4-ethoxyphenyl)acetamide], an analgesic and antipyretic agent, are reported. Available data from human case reports indicate that heavy use of analgesic mixtures containing PA is associated with papillary necrosis of the kidney. They suggest a relationship between this usage and the development of transitional cell carcinoma of the renal pelvis. Of 104 patients with chronic nonobstructive pyelonephritis who were heavy users of PA-containing analgesics, 8 developed transitional cell carcinomas of the renal pelvis and 2 developed bladder tumors; in 7, renal papillary necrosis was present. No tumors were seen in 88 control subjects not considered heavy users of analgesics. In one limited experiment in which PA was administered orally to rats, no carcinogenic effects were observed. However, 15/15 surviving rats fed a diet containing 0.05% N-hydroxyphenacetin, a putative PA metabolite, developed hepatocellular carcinomas, compared with 0/15 controls. (59 refs.)

77-0624 **The Effects of Long Term Feeding of Phenobarbital in Mice.** (Eng.) Jones, G.; Butler, W. H. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.;

Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. XVII, pp. 285-295; 1976.

The development, structure, and behavior of focal proliferative lesions induced in the livers of weanling male C3H mice by feeding a diet containing 1,000 ppm phenobarbital (PB) were studied by light and electron microscopy. Parenchymal cell nodular lesions arose in 74% of the PB-treated and 20% of the control mice during their life span. Small microscopic lesions were seen after 20 wk in test animals and after 44 wk in the controls. The morphology of the parenchymal cells in the lesions from the PB-fed mice differed from that in the controls, many of the nodules being characterized by the presence of hypertrophied cells with bizarre folded nuclei containing multiple nucleoli and inclusions. These cells also contained an abundant smooth endoplasmic reticulum, especially around the periphery of the cells, and microbodies were numerous. No lung metastases were identified in this series. The problem of defining malignant lesions in mouse liver is discussed. (13 refs.)

77-0625 **Phenobarbital and Phenobarbital Sodium.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 167-181; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are reported for phenobarbital [PB: 5-ethyl-5-phenyl-2,4,6-(1H,3H,5H)pyrimidinetrione] and its sodium salt (SPB). These compounds are used as hypnotics and sedatives and in the treatment of epilepsy. SPB was carcinogenic in mice and rats after lifetime oral administration. Both benign and malignant liver tumors were found in 24/30 male and 21/28 female CF1 mice killed after being fed for 109 wk with a diet containing 500 mg/kg SPB. Similar tumors were seen in only 11/45 male and 10/44 female control mice. In Wistar rats administered SPB at a concentration of 500 mg/liter in drinking water, 13/22 males and 9/28 females had benign hepatic neoplasms at 152 wk of age; no such tumors were observed in control animals. However, the available evidence from human case reports and epidemiological studies was judged to be insufficient to allow evaluation of the carcinogenicity of PB in man. (107 refs.)

77-0626 **Phenylbutazone and Oxyphenbutazone.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances.* International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 183-199; 1977.

Chemical and physical data; production, use, occurrence, and

analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are reported for phenylbutazone (PB: 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione) and oxyphenbutazone (OPB: 4-butyl-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione). These anti-inflammatory agents are used in the management of gout, arthritis, and thrombophlebitis. Several cases of leukemia were reported between 1960 and 1966 in subjects treated with PB or OPB; however, the available evidence is judged insufficient to substantiate the suggestion that PB or OPB is related to the development of leukemia. No data concerning the carcinogenicity of PB or OPB in animal species are available. Significant increases in the number of chromosome abnormalities resulting from chromosome-breaking events were reported in cultured human peripheral WBC from patients with 100-500 mg/day PB for at least 3 mo for rheumatic disorders. (61 refs.)

- 77-0627 **Phenytoin and Phenytoin Sodium.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances*. International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 201-225; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data for phenytoin (PT: 5,5-diphenyl-2,4-imidazolidinedione) and its sodium salt (SPT), which are used in the management of epilepsy, are reported. An association has been observed in epileptic patients between the occurrence of lymphomas and long-term anticonvulsant therapy in which PT alone or in combination with other anticonvulsants was given. Of 516 patients with malignant lymphomas, 8 had received PT treatment, compared to only 2/516 tumor-free control patients. PT and SPT are carcinogenic in mice following ip or oral administration, respectively. Of 24 surviving female C57BL mice fed SPT at a dose level of 60 mg/kg body wt/day in a liquid diet for 168 days, 3 developed thymic lymphomas after 10 mo, but no pathological lesions were seen in 48 controls. Of 40 surviving albino mice that received 0.6 mg/day PT for 66 days, 10 mice developed tumors (4 thymic and 2 mesenteric lymphomas; 4 leukemias) after 9 mo; in 50 control mice, 1 thymic lymphoma and 1 lung adenoma were observed. (125 refs.)

- 77-0628 **Pyrimethamine.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances*. International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 233-242; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data for pyrimethamine [PM: 5-(4-chloro-

phenyl)-6-ethyl-2,4-pyrimidinediamine], an antimalarial agent, are given. In the only animal study available for evaluation, PM produced a significant increase (from 0.22 to 0.78) in the number of lung tumors per A/He mouse 24 wk after the injection of high ip doses (total, 0.125 g/kg in 5 injections over 8 wk). PM is teratogenic in rats and chickens, and a concentration of 1.5×10^{-4} g/ml in the feed of *Drosophila melanogaster* produced a three- to fourfold increase in the number of X-linked recessive lethal mutations. In man, PM crosses the placental barrier and is excreted in milk. Chromosome abnormalities were observed in metaphases of bone marrow cells examined in 3/5 patients receiving total doses of 200-300 mg PM. No data are available as to the carcinogenic effects of PM in man. (31 refs.)

- 77-0629 **Selenium Maligned Again (Letter to Editor).** (Eng.) Schrauzer, G. N. (Dept. Chemistry, Univ. California, Revelle Coll., La Jolla, CA 92093) *Chem Eng News* 55(19): 2; 1977.

In long-term feeding experiments, Se was administered to mice at dosage levels of 5.0 and 15 ppm in the drinking water. No sign of carcinogenicity was observed. On the contrary, Se exhibited a cancer-protecting effect. As with other essential trace elements, Se becomes toxic at higher than optimal concentrations, and 5 ppm of selenium in the drinking water does produce chronic Se toxicity. However, there is no evidence to support the claim that selenium is carcinogenic. (1 refs.)

- 77-0630 **Aurothioglucose.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Miscellaneous Pharmaceutical Substances*. International Agency for Research on Cancer (Lyon, France): Vol. 13, pp. 39-45; 1977.

Chemical and physical data; production, use, occurrence, and analysis; and available metabolic, mutagenic, toxicological, and carcinogenic data are provided for aurothioglucose [ATG: (1-thio-D-glucopyranosato)gold], which has been used in the treatment of rheumatoid arthritis and nondiabetic seminated lupus erythematosus. ATG was carcinogenic in mice in several experiments; for example, 21/34 male CBA mice developed hepatomas at 56 wk of age after ip treatment with 400 mg/kg of ATG when 13-14 wk old, whereas only 7/36 untreated animals developed hepatomas. The ip LD₅₀ of ATG is 2,000-2,500 mg/kg in mice. Doses of 350 mg/kg to CBA mice caused bilateral hypothalamic lesions associated with obesity; in C57BL mice, doses of 1,200 mg/kg were required to cause similar obesity. No data as to the carcinogenicity of ATG in man are available. (18 refs.)

- 7-0631 **Chloroform Toxicity (Letter to Editor).** (Eng.) Kay, K. (Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029) *Am Ind Hyg Assoc J* 38(2): A-24 - A-25; 1977.

The author criticizes a previous paper that covered tests of chloroform toxicity over 6 mo. During that time, as might be expected from what is known about chemical carcinogenesis, cancers did not develop. The report is misleading, because the question as to whether cancers might have developed over the longer exposure period used in the NCI chloroform tests was not answered. The noncarcinogenicity of chloroform in the 6-mo test may indeed be inconsequential in comparison with its carcinogenicity, as was the case with vinyl chloride. (no refs.)

- 7-0632 **Genetic Toxicology of Mitomycin C, Actinomycins, Daunomycin and Adriamycin.** (Eng.) Vig, J. K. (Nevada Mental Health Inst., P.O. Box 2460, Reno, NV 89505) *Mutat Res* 38(2): 189-238; 1977.

The genetic effects of mitomycin C (MMC), actinomycins (ACMs), daunomycin (DNM) and adriamycin (ADR) are reviewed. All these chemicals interact with DNA. MMC forms about cross-linking of the DNA strands and acts as a mono- and bifunctional alkylating agent. The other three intercalate with the DNA molecule. ACMs, especially CM-D, inhibit RNA synthesis preferentially and discriminate between different species of RNA. At high concentrations, DNA, RNA and protein synthesis are all inhibited by any of these antibiotics. The agents effect the cell-cycle traverse at various stages; MMC is the most unspecific of all. Mitotic cells at post-G₂ stages are the least effected by any of these chemicals. All these chemicals induce chromatid aberrations. The anthracyclines produce chromosome-type aberrations, perhaps by affecting the single-stranded G₁ chromosome. Rejoining occurs, but MMC creates a high frequency of quadriradial configurations by utilizing the analogous nucleotide sequences in the repetitive DNA. At other points, it creates chromosome fragments. The mechanisms appear to be different for induction of chromosome aberrations by MMC, ACT and the anthracyclines. The associated phenomenon of sister chromatid exchanges is strongly potentiated by these agents. MMC is a known mutagen in both akaryotes and eukaryotes; it also increases the frequency of meiotic recombination. CM-D induced aberrations are primarily of the chromatid type. MMC and ACM-D also induce somatic recombination and somatic mosaicism; MMC is a potent recombinogen. The data point to a great need for testing of chemicals for genetic toxicology; particular attention must be given to the subject of co-mutagenicity. Data enabling us to make rational decisions affecting the genetic health of our species are urgently needed. (354 refs.)

- 7-0633 **Significance of Vitamins in Cancer.** (Eng.) Basu, T. K. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey, England) *Oncology* 33(4): 183-187; 1976.

The clinical and experimental data concerning the significance of vitamin nutrition with cancer are discussed. Vitamin A deficiency is apparently associated with cancer of the stomach, nasopharynx, and respiratory tract. The low levels of vitamin A and β -carotene in patients with tumors of the alimentary tract may be due to low fat diets. The increased absorption of vitamin A in patients with brain tumors is due to the increased absorption of the vitamin in the presence of excess intestinal bile acid. The vitamin apparently inhibits the induction of cervical cancer and tumors of the respiratory tract induced by 7,12-dimethylbenzanthracene in rats. Vitamin A has prophylactic and therapeutic effects on development of chemically induced papillomas and carcinomas of the skin in mice. It enhances the effect of cyclophosphamide in mammary gland adenocarcinoma in rats and mice and of 1,3-bis(2-chloroethyl-1-nitrosourea) in leukemic mice. Vitamins B, particularly riboflavin, reduces the carcinogenicity of azo-dyes in rats. Spontaneous murine mammary carcinoma is dependent on the presence of pantothenic acid; cancer patients require an increased intake of folic acid. Some forms of chemotherapy may lead to a vitamin B complex deficiency. Mammary adenocarcinoma in the mouse is dependent on nicotinic acid. Malignant carcinoid causes excess tryptophan metabolism. Thiosemicarbazone (3-ethoxy-2-oxobutylaldehyde) is an active antitumor agent against several transplanted animal tumors. The majority of patients with malignant disease have minimal tissue stores of vitamin C. Breast cancer patients may have increased requirements for vitamin C, perhaps to maintain the increased turnover rate of bone collagen. Vitamin C may relieve patients of the pain of multiple skeletal metastases. It is concluded that one vitamin may act as an inducer for one kind of tumor but an inhibitor of another kind. (57 refs.)

- 77-0634 **Molecular and Genetic Basis of Furocoumarin Reactions.** (Eng.) Scott, B. R. (Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC 27709) Pathak, M. A.; Mohn, G. R. *Mutat Res* 39(1): 29-74; 1976.

The genetic and molecular basis of furocoumarin (FC) reactions is reviewed. FC compounds are useful in the treatment of vitiligo and psoriasis and in increasing the tolerance of skin to solar radiation in people who burn easily. Many investigators have shown that scheduled DNA synthesis is inhibited by photosensitization with FC's. FC's not exhibiting skin-photosensitizing activity, such as xanthotoxol, inhibit the incorporation of labeled precursors, the index used to measure DNA synthesizing ability. For the cases in which inhibition occurs, the degree of inhibition apparently depends on the concentration of the active FC, the dose of radiation exposure, the type of FC, and the type of biological material used. Different wavelengths of UV irradiation combined with 8-methoxypsoralen may result in both protection against and induction of UV-induced skin tumors in Swiss mice. The

molecular mechanism of photosensitization by the active FC's consists of a series of steps: molecular complexing, photobinding of FC's to DNA and bases, and cross-linking between strands of DNA. Skin-sensitizing FC's in combination with long-wavelength UV radiation induce point/gene mutations and chromosome aberrations in a variety of organisms. From these results, especially the chromosome aberrations induced in human cells in culture, it is likely that genetic alterations may also be induced in man. Because unmetabolized FC's do not appear to exhibit mutagenic properties without concomitant radiation, genetic alterations in adult human germinal cells will probably not occur because of the inability of the radiation to penetrate to these cells. Present evidence would tend to indicate that a therapeutic treatment regime of FC's combined with radiation is not hazardous to man. (295 refs.)

- 77-0635 Contemporary Animal Nutrition and its Potential Hazards to Human Health.** (Ger.) Somogyi, A. (Bundesgesundheitsamt, Institut für Veterinarmedizin (Robert von Ostertag-Institut), Postfach, D-1000 Berlin 33, W. Germany) Malick, L. E.; Langenbach, R.; Sallach, K. *Zentralbl Bakteriol [Orig B]* 163(1/4): 153-172; 1976.

Since new substances are continuously introduced into agriculture, it is necessary to reassess the requirements for the approval of compounds likely to appear in the food of man via the edible tissues of animals. Since a number of animal drugs and feed additives have recently shown carcinogenic potential, problems encountered while planning animal studies for the safety evaluation of chemicals are discussed. Metabolism of the test substance must be dealt with. Most carcinogens require metabolic transformation in order to react with macromolecules and so exert their biological action. Residues of many drugs in animal tissues appear to be various metabolites rather than the parent compounds themselves. It is not known whether many chemical residues are simply stored in different compartments of the organism as a result of their physico-chemical properties or whether they are covalently bound to vital macromolecules. Their biological significance is thus not quite clear. The enzyme system which metabolizes numerous drugs, pesticides, and endogenous and exogenous substrates is responsible for both the activation and detoxification of carcinogenic chemicals. The balance between these two processes of opposing toxicological consequence is determined by genetic and environmental factors. Depending upon the metabolic profile of chemicals, certain compounds are carcinogenic in one animal species while not in others. The manipulation of their metabolism by physiological or pharmacological means can result in a profound change of various biological actions of chemicals. To ascertain that potential toxicological hazards to human health by animal drugs and feed additives will be recognized during testing, appropriate test animals have to be selected with care. The metabolic break-down of the investigational substance must proceed via similar pathways in both test animals and the target species. (46 refs.)

- 77-0636 Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine.** (Eng.) Finklea, J. F. (Natl. Inst. for Occupational Safety and Health, 5600 Fishers Ln, Rockville, MD 20852) *Am Ind Hyg Assoc J* 38(3): A-21-A-23; 1977.

Recent studies are presented on the metabolism, toxicity, and carcinogenicity of phenyl- β -naphthylamine (PBNA). PBNA is used as an antioxidant in rubber manufacture. When PBNA (10 mg po) was given to 4 exposed workers and 19 volunteers, the 24-hr urine specimen showed β -naphthylamine (BNA) in excess of that expected from the known BNA contamination of PBNA. A limited epidemiologic study involving deaths among workers who entered the rubber industry after 1949, when BNA was replaced by PBNA, showed no significant excess risk of bladder tumor in industry. Three female dogs given PBNA (540 mg po/day for several yr) showed no bladder tumors after 4.5 yr. In mice fed PBNA for 18 mo, the incidence of hepatomas was significantly greater than in controls. BNA has also been found in the urine of dogs fed 2-nitronaphthalene. When 2-nitronaphthalene (100 mg/day \times 8 mo) was given to four female dogs, three dogs autopsied 10.5 yr later showed bladder papillomas in various stages of malignancy. (no refs.)

- 77-0637 Metabolic Precursors of a Known Human Carcinogen (Letter to Editor).** (Eng.) Moore R. M. (Natl. Inst. Occupational Safety and Health, 5600 Fishers Lane, Rockville, MD 20857) Woolf, B. S.; Stein H. P.; Thomas, A. W.; Finklea, J. F. *Science* 195(4276): 344; 1977.

The potential problem of the metabolic conversion of materials believed innocuous into known human carcinogens is considered. Concern about this problem was highlighted by recent findings that both N-phenyl- β -naphthylamine (PBNA) (a widely used rubber antioxidant) and 2-nitronaphthalene (a byproduct of α -naphthylamine production) are metabolized to the carcinogen β -naphthylamine (BNA). In a recent study, 3-4 μ g BNA were found in 24-hr urine samples from two volunteers who had ingested 50 mg PBNA and from workers estimated to have inhaled 30 mg PBNA. These findings indicate that PBNA is at least partially metabolized by the human body to BNA. An estimated 15,000 workers are at risk of exposure to PBNA during its manufacture and use. Another study has demonstrated that 2-nitronaphthalene is metabolized in laboratory dogs to BNA. There are no reports, however, concerning the metabolism of this compound in man. These studies have led to the following recommendations by the National Institute for Occupational Safety and Health: (1) more consideration should be given to the metabolism of chemical agents found in the workplace; (2) materials that can be metabolized by the human body to known carcinogens should be handled in the same way as carcinogens; (3) industrial hygiene practices should be followed to minimize exposure to PBNA; and (4) alternative antioxidants

to PBNA should be evaluated with regard to human effects. (3 refs.)

77-0638 **Dr. Gordan Replies (Letter to Editor).** (Eng.) Gordan, G. S. (Dept. Medicine, Univ. California, San Francisco, CA) *West J Med* 126(2): 153-155; 1977.

The author replies to a criticism of his dismissal of the notion that estrogen therapy in postmenopausal women causes uterine cancer. It is not correct that endometrial cancer is highly lethal. The type of cancer associated with estrogen therapy is likely to be detected early and at a curable stage, probably upon examination for uterine bleeding. In the studies cited in the criticism, 95% of the estrogen-associated cancers were stages 0 or 1 (atypical adenomatous hyperplasia or carcinoma in situ). Only one was associated with deep myometrial invasion. In contrast, 25% of the cancers not associated with estrogen were in higher stages and they were more deeply invasive. Estrogens are carcinogens, when given continuously in large doses to susceptible strains. Surprisingly small doses of estrogens (which rarely produce endometrial hyperplasia or bleeding) do, however, prevent the bone loss that results from menopause or oophorectomy. A large number of prospective studies has demonstrated that properly administered estrogens do not cause cancer. (16 refs.)

77-0639 **Estrogen Therapy in Postmenopausal Women (Letter to Editor).** (Eng.) Brown, S. M. (Dept. Epidemiology, Sch. Public Health, Univ. California, Berkeley, CA) *West J Med* 126(2): 151-153; 1977.

Issue is taken with a previous report, in which the notion that estrogen therapy in postmenopausal women causes uterine cancer was dismissed. The major argument was that the higher risk found in recent epidemiologic studies is a result of an increase in case findings due to increased diagnostic curettages, carried out because of estrogen-induced bleeding. Two papers were cited in which the controls were bleeders, and no estrogen-associated risk was demonstrable. Neither of those studies was population-based or carefully organized, epidemiologically. In both, most of the patients were selected before the massive use of estrogens. Finally, the requirement that controls be bleeders necessitated the inclusion of women with a variety of abnormal endometria. Such pathological entities might be precancerous and/or estrogen-induced. In any case, the controls would, under the estrogen-cancer hypothesis, have a falsely elevated proportion of estrogen-exposed women. If the theory of increased case findings were correct and the estrogen-cancer hypothesis were to be rejected, one would have to conclude that among normal postmenopausal women there is a large number of latent, subclinical, or undiagnosed uterine cancers, perhaps five to eight times the number ordinarily being diagnosed, that would be

found if these women underwent curettage. Until there is more convincing evidence that estrogens are not carcinogenic, however, the present author states that the clinical community should withhold estrogen therapy from all but the most severely ill patients. (37 refs.)

77-0640 **Rauwolfia Derivatives and Breast Cancer (Letter to Editor).** (Eng.) Christopher, L. J. (Aberdeen-Dundee Medicines Evaluation Monitoring Group, Ninewells Hosp., Dundee DD2 1UB, Scotland) Crooks, J.; Moir, D.; Weir, R. D. *Lancet* 1(8003): 140-141; 1977.

The possible association of rauwolfia derivatives (used to treat hypertension) and breast cancer was investigated using data from 879 cases of breast cancer and their controls. Each case was matched with an inpatient who had cancer (except breast cancer) and with a noncancer control. Analysis of the resulting 879 three-patient sets showed that in 765 rauwolfia had not been used; 104 sets had one-patient exposure to rauwolfia derivatives, 10 sets had two-patient exposures, and in no set were all three patients exposed. For sets with any exposure there was virtually a 1/1 ratio of observed to expected rauwolfia use. This study does not support the suggested association between rauwolfia derivatives and breast cancer, and the use of reserpine-type drugs cannot be discouraged on the grounds of carcinogenicity. (12 refs.)

77-0641 **Intrauterine Diethylstilbestrol Exposure and Its Consequences. Pathologic Characteristics of Vaginal Adenosis, Clear Cell Adenocarcinoma, and Related Lesions.** (Eng.) Robboy, S. J. (Dept. Pathology, Massachusetts General Hosp., Boston, MA 02114) Scully, R. E.; Welch, W. R.; Herbst, A. L. *Arch Pathol Lab Med* 101(1): 1-5; 1977.

Intrauterine diethylstilbestrol (DES) exposure and its consequences are assessed based on 300 cases accessioned in the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females. The association between prenatal exposure to DES and the subsequent development of clear cell adenocarcinoma and nonneoplastic abnormalities is established, but the mechanism of action of this drug is not clear. The evidence suggests that exposure must begin sometime between the 4th or 5th week and the 18th week of pregnancy. It is uncertain whether DES acts to stimulate the persistence of müllerian epithelium in the vagina or to inhibit its replacement by squamous epithelium. The tumors can involve all portions of the vagina and cervix. Almost two-thirds have been confined to the vagina; the remainder have been classified as cervical. The larger tumors in the vagina frequently involve much of its length and circumference, but the smaller ones are usually located in the upper third, most often in the anterior wall. The smallest tumor was 3 mm in greatest diameter, and the largest was > 10 cm. Most are polypoid and

nodular, but some are flat or ulcerated, with an indurated or granular surface. The cells of the clear cell adenocarcinoma can be detected cytologically, and, occasionally, a suspicious or positive smear may provide the first indication of an asymptomatic tumor. Nonneoplastic changes of the female genital tract associated with a prenatal exposure to DES include vaginal adenosis, cervical ectropion, and vaginal and cervical transverse ridges. Prenatal exposure to DES has not yet been linked to the development of any type of cancer in men. It is not clear whether DES is only a teratogen or, in rare instances, a carcinogen as well. It is also unknown whether the development of clear cell adenocarcinoma and adenosis is specific for DES and chemically related estrogens in contrast to steroidal estrogens. (23 refs.)

77-0642 Hormone Replacement Therapy and Endometrial Cancer. (Eng.) Anonymous (No affiliation given) *Lancet* 1(8011): 577-578; 1977.

The possible link between endometrial cancer and estrogens is discussed. Although epidemiological evidence is scarce, it is a fact that unopposed estrogen stimulation, either endogenous or exogenous, results in hyperplastic states of the endometrium that, in 12%-18% of cases, have been reported to progress to invasive disease. Withdrawal of estrogens or administration of antiestrogens can reverse or destroy these lesions. Screening techniques for women on estrogen replacement regimens are enumerated and discussed. (22 refs.)

77-0643 Hormonal Control of Mammary Cancer. (Eng.) Hilf, R.; Harmon, J. T.; Matusik, R. J.; Ringler, M. B. In: *Control Mechanisms in Cancer*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol. 1, pp. 1-24; 1976.

Biochemical alterations resulting from hormonal manipulation of the host were studied in rat mammary tumors. Tumors induced with 7,12-dimethylbenz(a)anthracene and R3230AC transplantable neoplasms were used. Pharmacologic doses of estrogens inhibited the growth of R3230AC tumors and reduced them by approximately 50%. The administration of estrogen also caused an intense secretory response in the tumor. Analysis of the fluid showed casein, lactose, some whey proteins similar to those found in rat milk, and significant amounts of short- and medium-chain-length fatty acids. These observations suggest that estrogen caused a lactationlike response in the tumor. Enzymes involved in lactation were also found in the tumor. Estrogen produced a dose related increase in glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme activities in the R3230AC tumor. The estrogen-induced response in G6PD was inhibited by actinomycin D, cycloheximide, or MER-25. Results indicated that estrogen is capable of stimulating G6PD synthesis. The estrogen-induced biochemical responses were accompanied by a decrease in growth rate sug-

gesting that hormone directed substrate utilization leading to differentiated products competed with substrate utilization for cell growth and proliferation. Treatment of breast cancer with progesterone has produced inconsistent results. Progesterone is able to inhibit lactogenesis in normal mammary gland and thus may prevent the differentiation and subsequent decrease in growth in the tumor. Androgens probably cause tumor inhibition by inhibiting carbohydrate metabolism and macromolecular synthesis. Prolactin, insulin, and cyclic nucleotides may also play a role in inducing biochemical alterations in rat mammary tumors. (115 refs.)

77-0644 Current Status of Melanocyte Chalone. (Eng.) Thornley, A. L.; Laurence, E. B. In: *Chalone*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 265-271; 1976.

A summary is presented of experimental evidence that suggests that melanocytes synthesize chalone (CH). One extensive study involved five daily injections of a 71%-80% ethanol precipitate of CH obtained from pig skin into Harding-Passey tumor-bearing mice and Green Fortner tumor-bearing hamsters. Optimal daily doses of 100-200 mg/mouse and 200 mg/hamster caused rapid tumor regression in 75 mice and 200 hamsters, but not spontaneous remissions in 1,000 and 3,000 untreated controls, respectively. However, a causal relationship between epidermal and/or melanocyte CH-induced mitotic inhibition and tumor regression was not subsequently proved. It is now known that the ethanol extract contains a powerful epidermal G₁ CH. A suggested invoked immune response has also not been proved. In conclusion, experimental evidence suggests that abnormal melanocytes derived from Harding-Passey and Green Fortner melanomas synthesize and respond to CH-like inhibitors of DNA synthesis (more specifically, inhibitors of isotopically labeled thymidine incorporation) and mitosis. (19 refs.)

77-0645 Ascites Tumours and Chalone. (Eng.) Bichel, P. In: *Chalone*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 429-449; 1976.

Studies of the growth of JB-1 ascites tumor in AKR mice suggest, at least partially, that this growth is controlled by negative feedback regulation, whose effect is exerted by humoral, chalone-like substances. Growth curves were determined after the ip injection of 2.5×10^4 ascites tumor cells. Cytokinetic analyses revealed that the decelerating growth with increasing tumor mass is brought about by a prolongation of the cell cycle and a decrease in the growth fraction. Colcemid was used in some of these studies. In accordance with a negative feedback hypothesis of growth, aspiration of most of the cells from the ascites tumor at the plateau phase was followed by a phase of regenerative or recurrent growth. Injections of cell-free ascitic fluid from these tumors at the plateau phase into mice carrying ascites tumors in recurrent

growth were followed by a transient arrest of the tumor cells in both the G_1 and G_2 phases. Ultrafiltration showed that the arrest of cells in G_1 and G_2 appeared to be caused by at least two different specific substances, probably proteins, with molecular wts of 10,000-50,000 and 1,000-10,000, respectively. (82 refs.)

77-0646 Epidermal Chalone in Experimental Skin Carcinogenesis. (Eng.) Elgjo, K. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 229-245; 1976.

In this survey, attempts are made to correlate data on experimentally induced growth alterations in mouse epidermis with variations in epidermal chalone (EC) content during the development of hyperplasia. A discussion is presented of the G_1 and G_2 chalones in relation to epidermal cell replication. Topical application of carcinogenic or noncarcinogenic hyperplasia-induced substances (including cantharidin and methylcholanthrene in benzene) leads to complex alterations in both epidermal metabolism and epidermal growth patterns. It is probable that the ability to produce EC is a function of cell age and differentiation, at least within a certain span of the life of an epidermal cell. Application of some tumor-promoting phorbol esters is followed by fluctuations in the epidermal level of cyclic AMP, which in turn could interact with EC to alter the rate of epidermal mitosis. With the increase in knowledge of how chalones influence normal growth, it is hoped that there will result a better understanding of how and why normal growth regulation breaks down during carcinogenesis. (40 refs.)

77-0647 Regulation of Cell Growth In Vitro and In Vivo: Point/Counterpoint. (Eng.) Attallah, A. M. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 141-172; 1976.

Existing growth regulation theories are compared with the concept of chalones (CH) as the preexisting endogenous specific inhibitors of growth. CH are also discussed in relation to various tumors. It is noted that lymphocyte CH in the presence of cytosine arabinoside and methotrexate was more cytotoxic to uncrowded L-1210 cells than crowded cells. Some hypothetical mechanisms involve contact inhibition and cell transformation, a "second messenger," and the cyclic AMP system. If CH is part of the cell membrane that regulates the cyclic AMP system, a simple model of growth regulation can be constructed. Diethylnitrosamine can permanently destroy CH activity. A unifying explanation would be that the CH glycoprotein contains two active sites: one specific for the cell membrane and the other nonspecifically stimulating the adenyl cyclase activity on the membrane. With adenyl cyclase activity, the intracellular concentration of cyclic AMP would be maintained at a relatively high level. The cell would then be unable to enter the mitotic cycle because of

a decrease in nucleoside kinase activity and, hence, a lack of DNA and RNA precursors. Since DNA synthesis requires the continuous recruitment of nucleoside precursors, it is speculated that CH shuts off the supply of precursors for macromolecular synthesis before the incorporation of deoxynucleoside triphosphates into DNA, but allows the completion of DNA synthesis from those triphosphates formed prior to CH addition. (115 refs.)

77-0648 The Epidermal Chalones. (Eng.) Marks, F. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 173-227; 1976.

The first part of this extensive review of epidermal chalones (EC) is a discussion of the evidence for feedback regulation of epidermal cell proliferation. In one study, when an impermeable implant was inserted into a wound in mouse skin, the epidermis migrated around both sides of the implant. After implantation of a porous filter, this only occurred after treatment of the skin with various carcinogens (but not after application of croton oil). Evidence is then presented for two EC: G_1 chalone, which inhibits DNA synthesis and G_2 chalone, which inhibits mitosis. For each of the chalones there follows a discussion on extraction, assay, purification and characterization, reversibility and tissue-specificity, hormones (and cyclic AMP in the case of G_2), and mechanism of action. One section deals with the actions of G_2 in other tissues. In a discussion of EC and hyperplasia, the first of three postulated functions of a chalone--inhibition of cell proliferation--is fairly well-established. Confirmation of the functions to delay maturation and to "decide" whether the cell divides again or enters the aging pathway have not yet been made. With reference to EC and carcinogenesis, three experimental epidermal tumors are known to contain G_2 chalone. The effects of dimethylbenzanthracene and methylcholanthrene on epidermal G_2 chalone are summarized briefly. (176 refs.)

77-0649 Biology of the Granulocyte Chalone. (Eng.) Rytomaa, T. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 289-309; 1976.

A review is presented of the biological characteristics of the granulocyte chalone (GC), a cell line specific, species non-specific, endogenous regulator substance that inhibits cell proliferation reversibly. Despite some early questionable results, subsequent studies clearly show that the action of GC is real and tissue-specific both in vitro and in vivo. GC, which inhibits cell proliferation in the transit populations of the granulocyte system, seems to act at the level of the cell membrane. It diverts cells from the G_1 phase to the G_0 phase with some direct or indirect effect on the S phase as well. GC is noncytotoxic and has no detectable effect on any tissue other than normal and leukemic granulocytes, even after long-

lasting in vivo treatment. It is concluded that GC offers an exciting potential for the treatment of myeloid leukemia. (80 refs.)

- 77-0650 **Bioassays and Tests for Chemical Carcinogens.** (Eng.) Weisburger, J. H. In: *Chemical Carcinogens. American Chemical Society Monograph 173*. Searle, C. E., ed. (Washington, D.C.: American Chemical Society): pp. 1-23; 1976.

The general requirements of bioassay systems for testing the carcinogenicity of chemicals for man are reviewed. A comprehensive bioassay in animals is best performed on more than one species, because even powerful carcinogens that affect man are not active in all species or in all strains of a single species. Animals that have recently been weaned (6-7 wk old) are usually used for bioassays. The mode of administration of the test chemical depends in part on the ultimate application and dosages of the chemical in the human environment and includes the following: po administration, cutaneous application, respiratory exposure, and sc, ip, and iv injections. It is important to select the correct max tolerated dose level, because it is expensive and wasteful to conduct tests on large groups of animals for long time periods only to discover that the dosages used were too low to give interpretable results. The number of animals used for definitive experiments may range from 25 males and 25 females per dose level to as many as 100 per group. In these experiments animals are maintained on test (1) until adverse effects are noted, (2) for 90 wk (mice) to 104 wk (hamsters and rats), or (3) for a lifetime. Complete and careful record-keeping and the advice of statisticians are necessary for proper interpretation of results. Transformation of cell cultures and mutagenicity tests may serve as prescreens for more definitive experiments. Sedimentation analysis of DNA and DNA repair synthesis may provide direct evidence for an alteration of DNA. Bioassays are being developed to detect fetal proteins that appear in the blood long before cancer is apparent. (111 refs.)

- 77-0651 **Environment and Cancer.** (Cro.) Cicek, J. (No affiliation given) *Libri Oncol* 5(2): 45-48; 1976.

The major carcinogens found primarily in water and air are enumerated. The attempts of the NCI and the Environmental Protection Agency to identify the geographic areas that are most affected by industrial pollutants are surveyed. The author stresses the need for identifying, classifying, and evaluating primary and secondary carcinogens. (no refs.)

- 77-0652 **Chemical, Viral, and Co-carcinogenesis.** (Eng.) Littlefield, J. W. In: *Variation, Senescence and Neoplasia in Cultured Somatic Cells*. (Cambridge, MA: Harvard Univ. Press): pp. 88-98; 1976.

The establishment of permanent cell lines via chemical carcinogens or oncogenic viruses and the phenomenon of cocarcinogenesis are reviewed. The first systemic study of in vitro carcinogenesis involved the use of 3-methylcholanthrene or benzpyrene with hamster cell cultures. After 3 wk of exposure, neoplastic transformation was observed; in addition, these tumors could be implanted for in vivo growth. Hamster cells were selected because of their low incidence of spontaneous transformation. Various hydrocarbons have induced fibrosarcomas in mouse cell cultures. Likewise, rat liver cells have been induced by the carcinogen 5-nitroquinoline. Human diploid cell lines have heretofore been found resistant to chemical carcinogenesis. Some viruses, eg polyoma, have been shown to cause neoplastic transformation in cells in some species and cytopathic effects (but not transformation) in others. The viral genome must be expressed in order for the transformed cells to be maintained. Diploid human cells have been transformed by the DNA viruses simian virus 40 (SV40), Epstein-Barr virus, and some adenoviruses. The SV40 genome has been localized to chromosome number 7. A marked additive carcinogenic effect is observed with oncogenic viruses and genetic factors (eg, Fanconi's anemia, Down's syndrome) predisposing to cancer. This combination is known as cocarcinogenesis. Chemicals and radiation can also act as cocarcinogens. Speculations regarding the resistance of human cell lines to transformation are presented. (no refs.)

- 77-0653 **Sequences and Functions of Rous Sarcoma Virus RNA.** (Eng.) Duesberg, P. H. (Virus Lab. and Dept. Molecular Biology, Univ. California, Berkeley, CA 94720) Wang, L. H.; Beemon, K.; Kawai, S.; Hanafusa, H. *Haematol Bluttransfus* 19: 327-340; 1976.

The genetic elements of avian tumor virus RNA, which has a molecular wt of about 3×10^6 daltons and a poly(A) sequence at the 3' end, were mapped. About 30 RNase T₁-resistant oligonucleotides were ordered relative to the 3' poly(A) terminus of the RNA in order to construct an oligonucleotide map of viral RNAs. A cluster of seven envelope-specific oligonucleotides, which were identified by their absence from the otherwise very similar oligonucleotide map of an envelope-defective deletion mutant (which lacks the major viral glycoprotein) were mapped at a distance of $0.9-1.6 \times 10^6$ daltons from the poly(A) end of sarcoma virus RNA. Another cluster of three sarcoma gene-specific oligonucleotides, which were identified by their absence from the otherwise nearly identical oligonucleotide map of a transformation-defective deletion mutant were mapped at a distance of $0.2-0.6 \times 10^6$ daltons from the poly(A) end of sarcoma virus RNA. The oligonucleotide maps of sarcoma viruses and of related deletion mutants were the same from

poly(A) end up to 0.2×10^6 daltons and included one terminal oligonucleotide, termed C, which is found in all avian tumor viruses tested so far. Preliminary mapping experiments ordering the sarcoma gene-specific and envelope gene-specific oligonucleotides of recombinants, selected for sarcoma and envelope genes of different parents, agreed with those obtained by comparing maps of wild type viruses and deletion mutants. A partial genetic map consistent with these results suggests that the sarcoma gene maps between the envelope gene and the 3'-poly(A) end of viral RNA. The map reads: poly(A)-sarcoma gene-envelope gene-(viral DNA polymerase gene and viral group-specific antigen gene). (19 refs.)

77-0654 Transport Changes Associated with Growth Control and Malignant Transformation. (Eng.) Veber, M. J. (Dept. Microbiology, Univ. Illinois, Urbana, IL 61801) Hale, A. H.; Yau, T. M.; Buckman, T.; Johnson, M.; Brady, T. M.; La Rossa, D. D. *J Cell Physiol* 89(4): 711-722; 1976.

The rate of uptake of nutrients and ions in chick embryo fibroblasts that were either density-inhibited, growing exponentially, or transformed by Rous sarcoma virus was determined. When normal growing cells were compared to transformed cells, only one change was detected: uptake of 2-deoxyglucose and 3-O-methylglucose was increased three- to fivefold in the transformed cells. ^3H -ouabain binding showed that there were fewer ouabain binding sites on the density-inhibited cells than on the growing cells. The uptake of ^3H -2-deoxyglucose was measured at temperatures from 13 to 0 C, and the data were utilized to construct Arrhenius plots. The slope of the plot was steeper for the transformed cultures than for the normal cultures. To examine the time course of appearance of the tumor virus-induced fatty acid alterations, the temperature-conditional mutant of Rous sarcoma virus (RSV-T5) was used. Chick cells infected with RSV-T5 and held at 36 C had a transformed phenotype and had a fatty acid composition typical of transformed cells, but the culture held at 41 C had a normal phenotype and a normal-type fatty acid composition. At time zero, cultures were shifted to the opposite temperature. At 10 and 26 hr after the shift, cultures were taken for analyses. Although the switch in the capacity to take up 2-deoxyglucose was complete within 26 hr, the changes in fatty acid composition were less than half complete. The addition of proteases (including plasmin) to normal, density-inhibited cultures did not stimulate them to take up 2-deoxyglucose at a rate much above that characteristic of normal, growing cells. Addition of dibutyl cyclic AMP to cells transformed by RSV-T5 restored the transformed level of 2-deoxyglucose uptake to normal. The results indicate that there are two classes of transport control in cultured chick cells. (50 refs.)

77-0655 In Vitro and Preliminary In Vivo Studies of Compounds Which Induce the Differentiation of

Friend Leukemia Cells. (Eng.) Preisler, H. D. (Roswell Park Memorial Inst., Dept. Medicine A, Buffalo, NY 14263) *Hematol Bluttransfus* 19: 161-167; 1976.

In vitro and in vivo studies of chemical agents that induce the differentiation of Friend leukemia cells (FLC) are reported. The cryoprotective agents tetramethylurea, dimethylacetamide, N-methylacetamide, pyridine N oxide, dimethyl sulfoxide, dimethyl formamide, acetamide, dimethylurea, pyridazine, and diethylene glycol showed differentiation-inducing potencies (% of benzidine positive cells after 5 days of culture in the presence of the inducing agent) in FLC (line 745A) cultures ranging from 7% to 70%. All of these agents are small, polar, freely diffusible compounds. Although the compounds varied widely in their inducing potency, the biology of the differentiation process, once begun, appeared to be the same regardless of the inducing agent used. The differentiation of FLC in vitro was accompanied by the accumulation of globin messenger RNA, and it appears that any stimulus that induces FLC differentiation ultimately acts through the process of transcription. The ability of inducers to cryoprotect RBC suggests that these compounds also have significant effects on the cell membrane. Using differential scanning calorimetry, inducing cryoprotective agents were found to increase the melting temperature of artificial acidic phospholipid vesicles, indicating a decrease in the fluidity of the vesicle membranes. It appears that the initial event during the induction of differentiation by cryoprotective agents may occur at the cell surface, with transcription being a necessary but secondary phenomenon mediated perhaps by communication between the cell membrane and the nucleus. Initial studies involving the inoculation of FLC lines 745A into syngeneic DBA2/J mice followed 1 wk later by the daily administration of the cryoprotective agent N-methylacetamide resulted in a significant and consistent inhibition of FLC proliferation in the spleens of treated mice and to a lesser extent the inhibition of leukemic cell proliferation in bone marrow. The induction of leukemic cell differentiation in vivo may provide a mode of therapy for leukemia. (29 refs.)

77-0656 Genetic Influence in Murine Viral Leukemogenesis. (Eng.) Meredith, R. F. (Viral Oncogenesis Section, Cancer Res. Unit, Clinical Radiation Therapy Res. Center, Div. Radiation Oncology Allegheny General Hosp., 320 East North Ave., Pittsburgh, PA 15212) *Biomedicine* 24(6): 374-380; 1976.

A gene that exerts a major influence of susceptibility to leukemia virus is the major histocompatibility locus, H-2. This gene is involved in all murine leukemia viruses for which H-2 influences have been studied, but not in murine sarcoma viruses. H-2 has a significant effect on the regression rate of leukemia-induced splenomegaly but little effect on the early aspects of viral leukemia expression. The expression of surface antigens on the infected spleen cells in Friend's disease is a complex function of time that appears to be H-2-

dependent. H-2 seems to be a universal factor augmenting other host leukemogenesis genes. Aside from genes known to govern susceptibility to leukemogenic viruses directly, other host genes exist that are regulatory or that influence leukemogenesis but have separate major functions unrelated to the leukemias themselves. There is a gene product in nonpermissive cells that actively inhibits some early postpenetration event(s) necessary for effective viral infection. On the other hand, studies of the lymphatic leukemia virus component of the Friend-Moloney-Rauscher viral complex have shown that host restrictions of viral replication may occur at a different time. In vivo experiments have demonstrated that susceptibility may be controlled through indirect means mediated by immune relationships and other factors involved in the basic regulations of hematopoiesis. In vitro experiments show that there are controlling effects directed by the prospective target cells in which effective virus infection and/or replication is inhibited. A significant amount of information is rapidly accumulating to explain the complicated gene influence on murine viral leukemogenesis. (52 refs.)

- 77-0657 Glucocorticoid Control of Gene Expression.** (Eng.) Kenney, F. T. In: *Control Mechanisms of Cancer. Progress in Cancer Research and Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol. 1, pp. 25-35; 1976.

The concept that glucocorticoids (GC) function at the nuclear level to control the expression of specific genes is discussed. Experiments concerning the induction of tyrosine aminotransferase (TAT) in liver or hepatoma cells and leukemia virus activation on mouse cells are also reviewed. GC promote specific transcriptions, since synthesis of specific proteins is increased by these hormones, messenger RNA coding for these proteins accumulates in GC-treated cells, synthesis of RNA is required, and the steroid must interact with the site of RNA synthesis before induced protein synthesis begins. Three Morris hepatomas were studied to determine if loss of sensitivity to hormonal control in tumors is due to loss of the receptor protein. The hepatomas were 7800, in which TAT is present but cannot be induced by GC. Glucose gradient analysis showed that all three contained readily detectable amounts of GC receptor. The binding capacity of receptors from each of the hepatomas was similar to that of the liver receptor, and all of the receptors were translocated to liver nuclei with comparable efficiency. Therefore, the nonresponsiveness of hepatomas 9633 and 9618A with GC cannot be attributed to a defect in the receptor system. Leukemia virus activation in mouse AKR cells by iododeoxyuridine (IUDR) was dissociated into two phases: incorporation of IUDR into DNA and synthesis of viral protein. Hydrocortisone had no effect when added in the first stage but was fully effective when added in the second. Hydrocortisone cannot replace IUDR as activator. Therefore, the steroid clearly modulates the expression of genes activated by IUDR substitution into DNA. (27 refs.)

- 77-0658 Genetic, Endocrine, and Viral Aspects of AKR Leukemogenesis.** (Eng.) Vriend, J. (Dept. Anatomy, Univ. Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio TX 78229) *Med Hypoth* 2(6): 257-261; 1976.

Viral, genetic, and endocrine aspects of leukemogenesis in AKR mice were evaluated. A derepression of the murine leukemia virus genome, which is integrated into the host cell genome, presumably occurs, along with some cell genes of the host genome, during the normal differentiation processes of a lymphocyte stem cell. Endocrine function of AKR mice is postulated to affect cellular enzymes associated with RNA in such a way as to stimulate expression of the viral genome at the expense of other specific regions of the host cell genome. During development, classical hormones, under genetic and environmental influence, cause prolonged expression of viral regions of the host genome. The reports of deficiencies associated with the H-2 region of linkage group IX are interpreted as a result of the presence of a polymerase enzyme with altered specificity. The postulated altered specificity of a host polymerase enzyme is regarded as specific enough to account for the apparent association of genes for virus-induced cell surface antigens and genes for host thymocyte products. The altered polymerase may or may not be associated with type C particles and could be an enzyme with a normal function during an early stage of development. It is predicted that by appropriate adjustment of the levels of hormones and cytokines during development, the AKR lymphoma, and leukemia syndrome and its associated deficiencies in growth, reproduction, and immunocompetence can largely be prevented. Induction of a polymerase enzyme and regulation of its action by hormones may favor the appearance of type C particles and the accumulation of undifferentiated lymphoid stem cells. (81 refs.)

- 77-0659 RNA Tumor Viruses.** (Eng.) Cardiff, R. D. (Dept. Pathology, Univ. California, Davis, CA 95616) *Chemistry* 50(4): 12-16; 1977.

The discovery of reverse transcriptase in RNA tumor viruses has lent major support to the provirus and oncogene theories of carcinogenesis. As predicted by the oncogene theory, mouse leukemia viral DNA has been detected in the cells of all mice tested using radioactive hybridization techniques, including mice in which leukemia is rare. The oncogene theory also predicts that expression of the viral gene is necessary to develop cancer and that animal cells can control virus DNA and keep it from being activated. Certain ordinary body functions may affect cancer growth through proviruses. Hormones that cause female mice to produce milk are also involved in causing breast tumors, and they may be mediated through mouse mammary tumor virus production. Genetic sequences for many tumor viruses have changed very little over millions of years, which may indicate that oncogenes are actually necessary and are kept intact to perform some as yet undetected function. Simply eliminating tumor viruses, there-

fore, might not be an ideal way to cure cancer. Virus particles have been detected in cells from human leukemia and breast tumor patients in tissue culture, but whether they are tumor virus particles and whether they cause the disease are unknown. (4 refs.)

- 77-0660 Interaction Between Viral and Genetic Factors in Murine Mammary Cancer: Possible Implications for Human Disease.** (Eng.) Hilgers, J.; Bentvelzen, P. In: *Breast Cancer: Trends in Research and Treatment. A Monograph of the European Organization for Research on Treatment of Cancer*. Heuson, J. C.; Mattheiem, M; Rozencweig, M., eds. (New York: Raven Press Books, Ltd.): pp. 3-9; 1976.

Results of studies conducted during the past 40-45 yr to investigate the various modes for transmission of murine mammary tumor virus (MTV) are summarized. In the early studies, an extrachromosomal factor was discovered that could be transmitted via the milk, transplacentally, via the male, who transfers the virus to the mother during mating (indirectly), via the male in utero, or via the male postnatally (directly). Besides this extrachromosomal vertical transmission, some evidence exists for horizontal transmission. More recently, chromosomal vertical transmission has been discovered. In GR mice, which have a high incidence of mammary tumors at an early age, the responsible gene may represent a DNA provirus. Molecular hybridization studies show that the normal cellular DNA of all the strains tested so far contains multiple copies of the MTV genome. Host factors may interfere with viral replication and thereby cause resistance to its oncogenic action. A specific gene system controlling viral carcinogenesis is the major histocompatibility locus of the mouse. Although most studies on host resistance have been concerned with an exogenous virus, some resistance factors to endogenous virus have been demonstrated. In humans, viruses transmitted as a genetic factor of the host may contribute to mammary carcinogenesis. (44 refs.)

- 77-0661 RNA Tumor Viruses and Breast Cancer.** (Eng.) Schochetman, G. (Meloy Lab., Springfield, VA) *Recent Results Cancer Res* 57: 21-25; 1976.

Recent research on the characteristics and detection of RNA tumor virus in experimental animals and human systems is discussed in relation to human breast cancer. In a study of mouse mammary tumor virus (MMTV), radioactive labeling and gradient centrifugation showed that the radioactive DNA-viral RNA complex sedimented in the 60-70 S region and at the density of RNA. RNA tumor viruslike particles or viral components from human breast tumors have been reported. Reverse transcriptase activity has been obtained from malignant human breast adenocarcinoma. Additional-

ly, molecular hybridization experiments showed that the RNA of human breast cancers contained nucleic acid sequences related to MMTV and to Mason-Pfizer monkey virus. Benign tumors and normal tissues did not hybridize with these viruses. Studies of homology between MMTV and resulting mouse tumors transmitted vertically and horizontally indicated that there are two classes of MMTV. The studies discussed indicate that RNA tumor-virus particles or components have been detected in human breast tumors. (19 refs.)

- 77-0662 Feline Mammary Gland Tumors.** (Eng.) Hayes, A. (Dept. Medicine, Animal Medical Center, 510 E. 62nd St., New York, NY 10021) *Vet Clin North Am* 7(1): 205-212; 1977.

The epidemiology, etiology, biological behavior and tumor morphology, therapy and posttherapy follow-up of mammary gland tumors (MGT) in the cat are reviewed. In a California study, the annual incidence was 12.8 per 100,000 cats (both male and female) and 25.4 per 100,000 female cooling and 30 min prior to irradiation, the cells were radioresistant. in the domestic shorthaired and Siamese breeds; however these breeds are the most common. Mouse mammary tumor virus has not yet been found in the cat. However, C-type particles and viral antigens have been demonstrated by electron microscopy and immunologic studies. In the cat all glands are susceptible; in 66% of 116 cats in one study both right and left gland-chains were involved. Surgery is currently the most common form of therapy. Most cats treated by surgery die of recurrent or metastatic disease or both. Better methods of treating feline MGT should be developed. (18 refs.)

- 77-0663 Viruses and Breast Carcinoma in Human Beings. Present Achievements and Prospects for the Future.** (Pol.) Dmochowski, L. (Dept. Virology, Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, TX 77025) *Nowotwory* 26(4): 249-272; 1976.

Viruses and breast carcinoma are reviewed. Breast cancer in women constitutes 11.8% of all common tumors in human beings, and 23.8% of all tumors occur in women. Breast cancer in humans is a multifactor disease whose formation depends on the joint action of genetic, hormonal, and environmental agents. The virus acts as an unblocking agent for the disease process; it in itself is not sufficient to cause the development of a tumor. It is concluded that morphological, biochemical, molecular, and immunological data, although suggestive, are insufficient to identify the viral etiology of breast carcinoma in humans. Recent investigations are examining the future application of antiviral antibiotics, such as a derivative of rifamycin and streptovaricin, to the chemotherapy of breast carcinoma in humans. (37 refs.)

- 77-0664 **Leukemia in Animals.** (Eng.) Winsser, J. (Natl. Cancer Cytology Center) *Cancer Cytol* 16(2): 28-31; 1976.

Characteristics of the various types of leukemias found in animals and the RNA tumor viruses known to cause them are reviewed. Different forms of leukemia can occur naturally or they can be induced in cattle, horses, subhuman primates, dogs, cats, mice, guinea pigs, rats, and fowl to varying degrees. The variegated clinical pictures are usually determined by the virus strain, the infective dose or doses, and the age and breed of the animal. Manifestations of several leukemia complexes such as bovine and avian leukosis are described. Although the RNA tumor viruses have been called oncornaviruses, they have also been named retroviruses because they possess reverse transcriptase, which translates RNA into DNA that, in turn, can become part of the cellular DNA. (no refs.)

- 77-0665 **Identification of Receptors for Animal Viruses.** (Eng.) Gallaher, W. R. (Dept. Microbiology, Louisiana State Univ. Medical Center, New Orleans, LA 70112) Howe, C. *Immunol Commun* 5(6): 535-552; 1976.

Cell surface receptors for each major group of animal viruses, and methods for studies of receptors, are reviewed. Hemagglutination, plaque formation, uptake of radioactively labeled virus and electron microscopy of attached virions are critically examined. The following classes of inhibitors have been used to define groups of viruses: (1) receptor analogs which compete with receptors for viral attachment; (2) lectins which compete with virions for attachment to receptors; and (3) enzymes which alter or destroy receptors. Both sensitive and resistant mouse and avian cell types have been shown to adsorb oncornaviruses. Interference between closely related oncornaviruses, particularly at the attachment step, can be demonstrated. Understanding and prevention of virus-receptor interaction is of obvious importance. (74 refs.)

- 77-0666 **The Role of Oncogenic Viruses in Neoplasia.** (Eng.) Klein, P. A. (Tumor Biology Unit, Dept. Pathology, Univ. Florida Coll. Medicine, Gainesville, FL 32610) Smith, R. T. *Annu Rev Med* 28: 311-327; 1977.

The role of viruses in animal and human cancers is reviewed. Leukemia is transmitted horizontally as a classical infectious disease by oncornaviruses in chickens and domestic cats, and, possibly, in inbred laboratory mice. No compelling epidemiologic evidence exists that either a horizontally or vertically transmitted virus is involved in any human leukemia, but some circumstantial evidence does support such an association. Evidence for the existence of a human analog of the mouse mammary tumor virus (MTV), which causes carcinoma in inbred mice, is found in nucleic acid hybridization experiments and in immunofluorescence tests with mouse

mammary tumor cells and sera from breast cancer patients and normal donors. Three groups of DNA-containing viruses, the herpesviruses, adenoviruses, and papovaviruses, have a proved oncogenic potential in animal systems. The herpesviruses have been implicated in the etiology of Burkitt's lymphoma, nasopharyngeal carcinoma, and cervical carcinoma. The adenoviruses have not yet been associated with any type of human cancer. Papovaviruses have been isolated from CNS tissue of patients with progressive multifocal leukoencephalopathy and have been shown to induce brain tumors in newborn hamsters. (117 refs.)

- 77-0667 **The Role of Viruses in Human Leukemia: A Summary.** (Eng.) zur Hausen, H. (Institut für Klinische Virologie, 852 Erlangen, Loschgestrasse 7, W. Germany) *Haematol Bluttransfus* 19: 475-480; 1976.

The role of viruses in human leukemia is discussed. The successful isolation of an oncornavirus that appears to share many characteristics with simian sarcoma virus from a patient with acute myelogenous leukemia has been reported. Despite the fact that the virus was repeatedly isolated from the same patient, there remains the possibility of laboratory contamination. An unidentified virus has also been isolated from a child with lymphosarcoma. Despite such isolations, there are certain features of most human leukemias which are presently difficult to reconcile with oncornavirus induction. In contrast to most animal oncornavirus-induced tumors, it appears to be extremely difficult to demonstrate any kind of oncornavirus-specific molecules in human leukemic cells. The sera from leukemic patients appear to lack antibody activities against known oncornaviruses. Also, human leukemias and lymphomas represent, at least in their vast majority, monoclonal disease; and the continuous production of transforming particles appears to be somewhat unlikely. There is no reason to speculate that human leukemias are herpes virus induced because virus-specific antigens within the transformed cell or on its surface have not been detected. Assuming that some forms of human leukemias have a viral etiology, it is speculated that they may be due to nonenveloped viruses. (23 refs.)

- 77-0668 **The GIX System in Relation to C-Type Viruses and Heredity.** (Eng.) Boyse, E. A. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021) *Immunol Rev* 33: 125-145; 1977.

The GIX system in relation to type C viruses and heredity is reviewed. If quasilinkage is the result of something affecting meiosis, then the frequencies of the four gametes AB:ab:aB:Ab should deviate from equal proportions. There should be an excess of two classes and a deficiency of the other two. If, quasilinkage has nothing to do with meiosis but is caused by superior fertilizing potency of 2/4 classes of gamete or occurs because 2/4 classes of progeny are better able to sur-

vive than the other two, then the four types of gametes should be formed in equal numbers. If two genes are chromosomally linked, they will not segregate independently in a backcross. The closer they are, the less they will be recombined by crossing over, the lower will be the frequencies of recombinant gametes, and the higher will be the proportion of nonrecombinant progeny with the same genotypes as their parents. However, sometimes backcross recombination data signify that two genes are linked when in fact they are on different chromosomes and so cannot be truly linked. There may be regions of attraction on nonhomologous chromosomes that create a tendency for them to travel together to the same pole at reduction-division. According to alternative models of affinity, the symmetrical halves of the meiotic framework on either side of the equator of the spindle are not identical. This polarity causes certain sets of nonhomologous chromosomes to be attracted to one pole of the spindle rather than to the other. The GIX:H-2 association constitutes quasilinkage and must be caused by nonidentity of alleles somewhere in the H-2 region. the GIX:Gpd-1 association also constitutes quasilinkage and must be caused by nonidentity of alleles somewhere in the Fv-1 region. Quasilinkage may be a special manifestation of type C viral genes. The outcome of genetic studies should allow a decision as to whether meiosis, zygosis, or embryogenesis holds the key to quasilinkage, and it may give a clue as to where to search for the suspected normal functions of type C genes and genomes. (29 refs.)

77-0669 **Cancer and Viruses.** (Eng.) Levine, A. J. (Moffett Labs., Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ 08540) *Chemistry* 50(4): 7-11; 1977.

The role of simian virus 40 (SV40) and adenoviruses in carcinogenesis is discussed briefly. Although adenoviruses contain more genetic information (30 genes) and organize it differently than SV40 (only 3 genes), about the same amount of genetic information in both viruses is involved in changing a normal cell into a malignant one. The first virus proteins synthesized by the cell under the direction of messenger RNA direct the cell to replicate viral DNA, and they are also responsible for changing the cell from normal to malignant. The virus need not complete both stages of replication, therefore, to produce a tumor. Viral chromosomes direct tumor cells to synthesize one or more viral proteins (tumor antigen, transplantation antigen), which might provide important diagnostic tools for human cancer in the future. Studies with SV40 temperature-sensitive (ts) mutants indicate that some viral genetic information directs the continuing synthesis of viral protein necessary for maintenance of the transformed state. A functioning viral protein also seems necessary for forming tumors in animals, but how this protein actually transforms cells remains a mystery. (1 refs.)

77-0670 **Senescence, Heteroploidy, and Neoplasia.** (Eng.) Littlefield, J. W. In: *Variation, Senescence, and Neoplasia in Cultured Somatic Cells.* (Cambridge, MA: Harvard Univ. Press); pp. 113-123; 1976.

Studies relating to the senescence of cell lines and to the transformation of cell lines to heteroploidy, with the unlimited growth of neoplasia, are reviewed. All diploid cells undergo senescence; however, through transformation to a heteroploid state (which may or may not be visible cytologically) the cell line may become "established"; ie, it will overcome senescence. In some cases, such as the 3T3 mouse cell line or human fibroblast cell lines infected with simian virus 40, some degree of growth control is maintained. Usually, however, the loss of growth control, or neoplasia, follows the process of establishment. The specific relationship between heteroploidy and neoplasia is unclear. The authors review various familial neoplastic diseases and familial conditions predisposing to neoplasia and briefly describe the known chromosomal aberrations identified with these diseases. (no refs.)

77-0671 **Type C Virogenes: Modes of Transmission and Evolutionary Aspects.** (Eng.) Todaro, G. J. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects.* Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag); pp. 357-374; 1976.

The possible involvement of type C RNA viruses in the etiology of human cancer is discussed. Type C RNA viruses have been isolated from many vertebrate species, and they have been shown to cause a variety of naturally occurring vertebrate neoplastic disease, including leukemias and sarcomas in chickens, lymphomas and related hematopoietic neoplasms and sarcomas in mice, lymphosarcomas and fibrosarcomas in domestic cats, and leukemias and sarcomas in some primates. Infectious primate type C viruses have recently been recovered from several colonies of gibbon apes with various hematopoietic neoplasms, especially myelogenous and lymphoid leukemias and from one woolly monkey with a spontaneous fibrosarcoma. Gibbon ape leukemia virus (GALV) and simian sarcoma virus-simian sarcoma associated virus (SSV-SSAV) spread from animal to animal under natural conditions and induce tumors when inoculated into other primates. Since these horizontally transmitted primate viruses are infectious and can cause tumors in primates, the possibility exists that this group of viruses may be involved in the etiology of human cancer. An enzyme with biochemical properties related to those of type C viruses and with antigenic properties similar to polymerases of the woolly monkey type C virus (SSAV) and GALV has been detected in human acute leukemia cells. The DNA products of endogenous reactions from the viruslike particulate fraction of acute leukemia cells hybridize preferentially to viral RNA from SSV and GALV. Using radioimmunoassays, antigens related to the major structural proteins (p30) of type C viruses have been detected in peripheral WBC from 5 patients with acute leukemia. A type C virus isolate, designated HL-

23, has recently been obtained from a cell culture derived from a woman with acute myelogenous leukemia, and this isolate appears to be closely related to the woolly monkey virus SSAV. A virus closely related to baboon type C viruses has also been isolated from this patient. Primates, including man, are known to contain endogenous type C viral sequences in their genome that are related to those found in endogenous baboon viruses. Endogenous virogenes may be partially expressed in humans and other primates, as evidenced by the detection of RNA sequences and antigens related to the p30 proteins of endogenous baboon viruses. The expression of endogenous viral-related antigens is found in carcinomas and lymphomas as well as in leukemias; viral p30 antigen expression has also been reported in certain normal human tissues. (63 refs.)

77-0672 Comment on Comparing the Membrane Transport Properties of "Normal" and "Transformed" Balb/3T3 Cells. (Eng.) Boone, C. W. (Cell Biology Section, Lab. Viral Carcinogenesis, NIH, Bethesda, MD 20014) *J Cell Physiol* 89(4): 757-758; 1976.

Properties of Balb/3T3 cells that should be taken into consideration when comparing the membrane transport properties of normal and transformed Balb/3T3 cells are discussed. The Balb/3T3 line produced tumors within 2-3 mo when an average of 3×10^4 cells were implanted sc attached to 1- x 5- x 10-mm polycarbonate platelets. The tumors were given a histological diagnosis of vasoformative carcinoma, because the tumor cells frequently formed vascular channels. The cultured tumor cells showed a loss of both postconfluence inhibition of proliferation and anchorage dependence. Evidence of the induction of endogenous oncornaviruses was obtained in only 1/4 tumors tested. Each of these tumors exhibited a tumor-unique transplantation-rejection antigen. These findings indicate that Balb/3T3 cells are derived, not from fibroblasts, but from vascular endothelial cells and that they constitute a population of preneoplastic cells in which spontaneous mutation to the condition of anchorage independence occurs at a relatively high frequency. Because of these findings, investigators should be judicious when making generalizations regarding the biological nature of cancer based on a study of Balb/3T3 cells and their derived transformed cell lines. Balb/3T3 cells are neither normal nor fibroblastic, and they differ from spontaneously transformed subclones principally in the specific property of anchorage dependence. (5 refs.)

77-0673 The Genome of Simian Virus 40. (Eng.) Kelly, T. J. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD) Nathans, D. *Adv Virus Res* 21: 85-173; 1977.

The molecular events involved in productive infection and transformation by simian virus 40 (SV40) are reviewed and

related to the structure and genetic organization of the SV40 genome. Emphasis is on the SV40 genome itself, its structure as a DNA molecule and a small chromosome, development of a physical map of the genome, its genetic content, its replication and transcription, and its interaction with cellular chromosomes. The characterization and biological properties of various SV40 mutants are also considered. In stably transformed cells, SV40 DNA, SV40 RNA, and T and U antigens are detected in all the progeny cells. An SV40-specific transplantation antigen is detected by biological tests. This indicates that SV40 genes persist in transformed cells, possibly integrated into the cellular chromosomes. The products of these genes (virion proteins and SV40-specific antigens) may be responsible for initiating and maintaining the transformed state. (319 refs.)

77-0674 Tumor Viruses and Cellular Gene Expression. (Eng.) Benjamin, T. L. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115) *Cancer Res* 36(11): 4289-4290; 1976.

During genetic studies on polyoma virus, a viral gene that appears to act by inducing the expression of certain cellular genes was identified. Mutants in this viral gene differed in two significant respects from wild-type viruses: they had a restricted host range, and they were unable to induce neoplastic transformation. Isolated originally on polyoma-transformed 3T3 cells as the permissive host, these mutants were subsequently demonstrated to be able to grow as well on type C RNA viral-infected 3T3 cells and on primary mouse embryo fibroblasts. The existence of permissive cells that did not carry integrated polyoma genes suggested that cellular functions were essential for virus replication and that it was the role of these hr-t viral gene to induce the expression of those essential cellular genes. The latter genes were expressed in normal embryo cells and in certain transformed cells, thus displaying features in common with carcinoembryonic antigens. The spontaneous loss of constitutive expression of the cellular permissive factor(s) was apparently counteracted by the action of the hr-t+ viral gene, causing these cellular genes to be reexpressed. Nineteen independent hr-t mutants were isolated. Hr-t mutants were unable to induce a cell surface alteration characteristic of transformed cells, and this could underlie their inability to cause neoplastic transformation. Marker rescue experiments demonstrated that a single wild-type viral DNA restriction enzyme fragment containing approx 13% of the viral genome could restore both a normal host range and transforming ability to the mutants. The hr-t viral gene could act to induce the expression of two classes of cellular genes, those involved in virus replication and those involved in transformation. Histones H-3 and H-4 derived from the wild type showed extensive acetylation compared to normal host cell chromatin, while the same two histone fractions from the hr-t mutant particles demonstrated little increase in acetylation over the host. The hr-t viral function may induce an altered, partially embryonic pattern of cellular gene

expression through a process that involves histone modification. (12 refs.)

- 77-0675 **Cell Transformation and Adenoviruses.** (Rus.) Nasz, J. (Inst. Microbiology, I. Semmelweis Medical Univ., Budapest, Hungary) Berencsi, D. *Vopr Virolog* (6): 643-650; 1976.

Cell transformation and adenoviruses are reviewed. The following aspects are dealt with: (1) structure of adenovirus DNA; (2) asymmetric replication and transcription of adenovirus DNA; (3) genetic differences among adenoviruses; (4) the adenovirus oncogenes; (5) location of the oncogenes in the chromosomes of a transformed cell; (6) integration of simian virus 40 (SV40) into the genome of adenoviruses; (7) adenovirus-SV40 hybrids; and (8) adenoviruses and malignant tumors in man. "Precursor" proteins of adenoviruses and their antibodies in human tumors could be demonstrated; they disappeared after the tumor was removed. It was possible to transform the viral gene responsible for cell transformation in vitro and to transform human cells by adenovirus. (63 refs.)

- 77-0676 **Preventing the Spread of Herpes Genitalis (Letter to Editor).** (Eng.) Yabrov, A. (Dept. Medical Microbiology, Banting Inst., Univ. Toronto, Toronto, Ontario, Canada) *Lancet* 8(8015): 809-810; 1977.

Measures are described for the control of herpes genitalis (HG). Control of HG may help to prevent the development of cervical cancer. Patients with chronic HG seem to be the main vectors for HG; special effort is required to identify all cases of chronic HG. To avoid missing carriers of potentially carcinogenic viral material, two measures must be undertaken: the isolation of naturally formed ts (temperature sensitive) variants of the virus capable of multiplying below 36 C, and the identification of incomplete (nonmultiplying and thus potentially carcinogenic) virus material. All the herpes virus which can cause genital infections in humans should be searched for, because all these have carcinogenic potential. In such investigations the male should be the first target. Carriers should be treated whether or not they have complaints or visible symptoms. (13 refs.)

- 77-0677 **New Properties of Mammalian Cells Transformed by Herpes Simplex and Cytomegaloviruses.** (Eng.) Rapp, F. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): pp. 61-470; 1976.

Evidence for the ability of herpes simplex viruses (HSV) and cytomegaloviruses (CMV) to transform mammalian cells in vitro is presented. Experiments involving a quantitative transformation assay using Swiss mouse 3T3 fibroblasts and ultraviolet-irradiated HSV-1 and HSV-2 revealed morphological transformation which was indicated by loss of contact inhibition. The number of foci were proportional to the dose of irradiation. The transformed colonies were of two morphological types: fibroblastoid or epithelioid. HSV antigens were observed by indirect immunofluorescence in both cell types. Support for the theory that CMV may induce neoplasia comes from observations which indicate that CMV can stimulate host cell DNA synthesis under permissive (human embryo lung cells) and restrictive (human embryonic kidney cells and monkey Vero cells) conditions. Heat-treated virus and UV-irradiated virus were unable to induce this stimulation. Morphologically transformed foci have been obtained when hamster embryo fibroblasts were exposed to UV-irradiated CMV. Virus-specific antigens were detected in the cytoplasm of 0.5% of the cells, while 47% yielded bright membrane fluorescence. Mixed hemagglutination assays and ¹²⁵I-labeled antiglobulin tests revealed that the virus-specific membrane antigen(s) present in transformed cells are similar to antigens found in CMV-infected human cells. The CMV-transformed cells were oncogenic on transplantation to animals, inducing fibrosarcomas. Normal human prostate cells (3-yr-old male donor) have yielded infectious virus upon early passages of in-vitro culture; subsequent passage of these cells has led to virus latency and persistence of the virus genome. Virus-specific antigens were observed in both the cytoplasm and on the membrane. Splenic lymphocytes from hamsters with CMV-specific tumors have been shown to be cytotoxic for the transformed human prostate cells, and molecular hybridization demonstrated 10-15 genome equivalents of CMV/transformed cell. All attempts to rescue the virus were unsuccessful. Long term cultures have now been established; these have maintained the diploid human karyotype, and preliminary results suggest that they may be oncogenic when transplanted into athymic mice. (58 refs.)

- 77-0678 **Oncogenic Potential of Herpes Simplex Virus in Mammalian Cells Following Photodynamic Inactivation.** (Eng.) Rapp, F. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Coll. Medicine, Hershey, PA 17033) Kemeny, B. A. *Photochem Photobiol* 25(4): 335-337; 1977.

The effect of photodynamic inactivation (used as a therapeutic technique in virus infections) on the oncogenic potential of herpes simplex virus (HSV) was investigated. HSV-1 and HSV-2 were replicated in cells pretreated with neutral red or they were directly treated with proflavine, neutral red, and methylene blue dyes before being exposed to normal fluorescent light. Hamster embryo cells exposed to proflavine-photoinactivated HSV-2 developed morphologically altered foci and loss of contact inhibition. Three clones that survived continuous passage contained HSV-specific antigens in the

cytoplasm and on the surface of the transformed cells. Attempts to isolate infectious virus from extracts of the transformed cells were not successful. One line of transformed cells was oncogenic in 6/7 newborn Syrian hamsters. The proflavine-treated HSV-2 transformed cells were less malignant than the neutral red-photoinactivated HSV-2-transformed hamster cells. These results suggest that treatment with a heterotricyclic dye, such as proflavine, and light allows differentiation between the lytic and transforming properties of human herpesviruses. They raise the question of whether the treatment of herpetic infections with photodynamic procedures warrants the possible increased risk of malignancy. (41 refs.)

- 77-0679 **Aetiology of Nasopharyngeal Carcinoma.** (Eng.) Anonymous (No affiliation given) *Lancet* 2(8000): 1393; 1976.

The etiology of nasopharyngeal carcinoma (NPC) is evaluated. Despite certain anomalies, the weight of evidence from Southeast Asia suggests that the greater the admixture of Chinese blood in a given ethnic group, the more likely it is that the NPC level in that group will be raised. Familial aggregations have been described for NPC among the Chinese, but the distribution is entirely random with both horizontal and vertical aggregates. Within a high-incidence area such as Hong Kong, there are regional variations in the incidence of NPC among different sections of the Chinese population. The principal exogenous factors to be considered are carcinogenic chemicals, either inhaled or ingested, and viruses. There is no clear association between occupation and NPC among the Chinese and, for the Chinese and also the Kenyans, attention has been concentrated on smoke in a domestic context, particularly in the use of grass or wood fires in poorly ventilated surroundings. The Chinese eat large amounts of salted fish, which contains diethyl- and dimethylnitrosamine. Diethylnitrosamine induces upper and lower respiratory tract tumors in hamsters, but the nitrosamine levels reported in preserved fish are extremely low. The association between NPC and Epstein-Barr virus (EBV) is extensively documented, but its evaluation is still unclear. Recent work suggests that the EBV genome in NPC cells and in cells from Burkitt's lymphoma may differ. The problem is to link a ubiquitous and predominantly nononcogenic virus with a tumor that has striking ethnic and geographic features. An undefined cocarcinogenic role for the virus appears to be the only solution. It is likely that several risk factors will vary in rank in the different groups in which NPC may arise. (11 refs.)

- 77-0680 **Evidence for an Etiologic Relation of the Epstein-Barr Virus to Human Malignancies.** (Eng.) Henle, W. (Joseph Stokes, Jr., Res. Inst., Children's

Hosp. Philadelphia Sch. Medicine, Univ. Pennsylvania Philadelphia, PA 19104) *Laryngoscope* 87(4): 467-473; 1977

The evidence for an etiologic relation of the Epstein-Barr virus (EBV) to human malignancies was examined. Antibodies to early antigens were found, with few exceptions, only in patients with EBV-associated diseases or with immunosuppressive conditions that may activate the latent, persistent viral carrier state that regularly ensues after primary EBV infections. The detection of EBV in oropharyngeal secretions of patients by its capacity to transform cord blood lymphocytes or the establishment of permanent cultures from infectious mononucleosis WBC provide confirmatory evidence, but they do not prove primary EBV infections. Since Burkitt's lymphoma is a monoclonal tumor, the EBV genome must have been in the first malignantly transformed cell. It has not yet been established whether the EBV-specific immunoglobulin A (IgA) antibodies in nasopharyngeal carcinoma originate from the secretory immune system or whether the IgA antibodies are derived from the systemic immune system. EBV is intimately associated with the essentially endemic type of Burkitt's lymphoma and with nasopharyngeal carcinoma, yet the exact role of the virus in the genesis of these two malignancies remains uncertain. (12 refs.)

- 77-0681 **Is Burkitt's Lymphoma Related to Perinatal Infection by Epstein-Barr Virus?** (Eng.) De-The. G. (Unit Biological Carcinogenesis, International Agency Res. Cancer, 150 Cours Albert-Thomas, 69372 Lyons Cedex 2, France) *Lancet* 1(8007): 335-337; 1977.

The possible relationship between Burkitt's lymphoma (BL) and perinatal infection by Epstein-Barr virus (EBV) is described. Primary EBV infection (demonstrated by the presence of viral capsid antigen, VCA, antibodies) occurs in Uganda in the first 2 yr of life and reaches 100% by the age of 3. In Singapore, the infection takes place at 3-4 yr of age in both ethnic groups (Chinese and Indo-Pakistani), and approx 20% of the 5- to 9-yr-old children are still seronegative. The geometric mean titer of antibodies to VCA reaches a peak of 421 in Ugandan children during the second year of life (a value similar to that observed for BL patients). This high peak in VCA/geometric mean titer is not observed in Chinese or Indian Singaporeans. Antibodies to early antigen, a marker of active EBV infection, are seen in 20% of Ugandan children aged 1-3 yr and 40% of Singaporean children aged 4-10 yr. The very early EBV infection observed in Uganda may represent a risk factor for BL development. The results imply an unusually long and persistent EBV infection (possibly perinatal in origin) in those children who will develop BL. If neonatal EBV infection is an important risk factor for BL development, the prevention of the lymphoma may depend on improvement in maternal health and infant care. Malaria has been proposed as a factor associated with BL risk. A sequence of events involving neonatal EBV infection,

heavy malaria burden, and possibly other environmental and host factors appears to be required to provoke BL development. It is proposed that perinatal infection (either transplacental or, more probably, neonatal) is a significant risk factor for the development of BL. (42 refs.)

77-0682 **Burkitt Lymphoma (BL), Virus-induced Malignancy?** (Eng.) Klein, E. In: *Burkitt Lymphoma, Hemostasis and Intercellular Matrix: Barbara Robert Memorial. Frontiers of Matrix Biology*. Robert, A. M.; Robert, L., eds. (New York: S. Karger): Vol. 3, pp. 1-14; 1976.

The relationship between Epstein-Barr virus (EBV) and Burkitt's lymphoma (BL) is reviewed. EBV causes infectious mononucleosis, which can be regarded as a self-limiting lymphoproliferative neoplasia. EBV-infected cells express several antigens against which antibodies are detected in human sera. Among the various human tumors tested for the presence of the EBV genome and EB nuclear antigen (EBNA), only African BL and nasopharyngeal carcinoma were positive. In contrast to the correlation between EBNA and the EBV genome, the serologically detectable cell-surface antigen (MA) is not detected in all genome-carrying cells. Antibodies reacting with viral capsid antigen are present in the serum of most healthy individuals, indicating the widespread presence of the EB virus. The seroepidemiology resembles that of other horizontally transmitted viruses. The majority of BL show a karyotype anomaly detectable both in in vitro cell lines and biopsies, indicating that transformation into BL is probably caused by a second, perhaps EBV-unrelated, event. In view of its demonstrated direct oncogenicity in monkeys and its highly efficient transforming ability in vitro, it is doubtful that EBV needs a helper virus. It is likely, however, that it requires a special form of cellular competence, perhaps a genetic deficiency in some regulatory mechanism, before fully autonomous malignant cells can emerge. (55 refs.)

77-0683 **Herpesviruses--A Link in the Cancer Chain?** (Eng.) Hollinshead, A. C. (George Washington Univ. Medical Center, Washington, DC 20037) Knaus, W. A. *Chemistry* 50(4): 17-21; 1977.

The prevalence, properties, and effects of herpes simplex virus (HSV) types 1 and 2 and their possible link to cancer are discussed. HSV 1 infects 90% of the adult population and HSV 2 infects 60%. There is indirect evidence that herpesviruses play a role in human cancer. Women with cervical cancer have consistently demonstrated more exposure to HSV-2 than have women without this tumor. Antibodies to two herpes tumor-associated antigens have been found in the blood of women with cervical cancer. One of these antibodies has been found in all patients with cervical cancer at diagnosis, but it disappears after successful treatment. Other herpes tumor-associated antigens have been found in the blood from 90% of patients with certain head and neck tumors. Because

HSV-1 infections occur in this part of the body, HSV-1 may also be linked with cancer. Epstein-Barr virus (EBV), which belongs to the herpes family, is definitely associated with African Burkitt's lymphoma. However, EBV is common in the US, where Burkitt's lymphoma is rare, suggesting that EBV by itself does not cause cancer. Possible vaccination against HSV-1 and HSV-2 is ill-advised, since killed forms of both viruses are capable of tumor production. (no refs.)

77-0684 **Strategy for Detection of Cancer Hazards to Man.** (Eng.) Doll, R. (Dept. Medicine, Univ. Oxford, Oxford, England) *Nature* 265(5595): 589-596; 1977.

A strategy for the detection of cancer hazards to man is presented. Like iatrogenic hazards, occupational hazards cannot have been responsible for more than a very small proportion of all cancers, since the total number of men who have been exposed in the course of their work is small in proportion to the population as a whole. If viruses do, in fact, cause cancer, they may do so only by interacting with other factors, and this may account for the separate correlation of hepatitis B antigen and aflatoxin with hepatoma and of the Epstein-Barr virus and gross malarial infection with Burkitt's lymphoma. Two different agents can interact to produce cancer, as established by occupational studies that have demonstrated interactions between smoking and asbestos and smoking and ionizing radiations and have provided quantitative data like those on the incidence of lung cancer in US uranium miners. Cancers of the stomach, colon, rectum, breast, and uterus have been common for many years, so that if they are environmental in origin, as the evidence suggests, the responsible factors must have been prevalent before the beginning of the century. Factors related to diet, which have been suspected of contributing to the production of cancer for many years, are enumerated. (54 refs.)

77-0685 **Oncoviruses and Cell Membrane Antigens.** (Eng.) Weiss, R. (No affiliation given) *Nature* 267(5606): 13; 1977.

Recent studies on the expression of endogenous antigenic glycoproteins of oncoviruses in cellular differentiation are reviewed. Pertinent findings are: 1) feral mice and jungle fowl express viral antigens, suggesting that there is no natural selection against viral antigen synthesis; 2) oncovirus envelope glycoproteins are detectable in a variety of avian species; 3) glycoprotein (gp 70) molecules associated with normal mouse tissues may be divided into groups related to gp 70 specificities of virus isolates. Cellular membrane proteins can be assembled into virus envelopes. Stomatitis virus grown in mouse cells incorporated H-2 antigen, and Friend virus particles selectively incorporated H-2Db antigen. The use of complexes of viral and cellular glycoproteins as potent immunogens is suggested. (11 refs.)

77-0686 Relations Between H-2 Complex, Tumor Antigens and/or Virus-induced Antigens. (Fre.)

Levy, J. P. (Laboratoire d'Immunologie et de Virologie des Tumeurs, INSERM U 152, Hopital Cochin, 75014 Paris, France) *Ann Immunol (Paris)* 128C(1/2): 493-505; 1977.

The theory that modification of the H-2 antigens is responsible for their appearance on the surface of tumor cells and/or cells infected by virus agrees with the concept of immune surveillance, but has only recently been supported by experimental evidence. In this review, the role of the H-2 antigen in immune response is evaluated. Recent evidence suggests that cytolytic T lymphocytes recognize and react with the H-2 antigens of the tumor cell. Experiments defining the specific H-2 regions with which the T lymphocytes interact are discussed. It appears probable that the H-2 antigens play a role in the immune surveillance of virus-induced tumors, but there seems to be no evidence for a link between H-2 and tumor antigens in chemically induced neoplasms. (101 refs.)

77-0687 Tumor-associated Antigens. (Eng.) Ristow, S.; McKhann, C. F. In: Mechanisms of Tumor Immunity. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 109-145; 1977.

The role of tumor-associated antigens in the tumor-host interaction is reviewed. Since tumor-associated antigens have been demonstrated by transplantation and serological techniques, the extraction and purification of these molecules have become significant. Assays for tumor antigens fall into three general categories: in vivo, in vitro using cellular immunity, and in vitro using antibody. The highly tumor-specific antigen may be responsible for tumor rejection, but the shared antigens, presumably of embryonic origin, are not. In addition to its capacity to interfere directly with the interaction between immune lymphoid cells and tumor cells, circulating antigen may exert a central depression on the immune response, inducing tolerance. In virus-induced tumors, there may be a direct relationship between the antigen and the cause of the malignancy. The form in which the antigen is presented to the immune system and the mechanism by which it is handled are significant factors in determining the extent and nature of the immune response. (315 refs.)

77-0688 Cell-Mediated Immunity to Leukemia Associated Antigens in Experimental Models and in Man. (Eng.) Herberman, R. B. In: Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): pp. 195-206; 1976.

The detection of cell-mediated immune reactions against leukemia-associated antigens in experimental animal models and

in patients with acute leukemia is discussed. Inhibition assays of the specificity of cell-mediated reactivity induced in W/Fu rats by Gross leukemia virus have revealed an antigen associated with rat endogenous type-C virus. An antigen related to the expression of mouse endogenous type C virus has been found in mouse cells transformed with murine sarcoma virus. Cytotoxicity assays of cell-mediated immunity against a Friend virus-induced leukemia (FBL-3) have indicated reactivity against the FMR serologic specificity and also against MEV-SA-1. T-cell cytotoxic responses in each of the above three animal model systems were considerably lower in progressor animals than in regressors. In growth inhibition assays, more reactivity was seen in progressors than in regressors, and the activity appeared to be correlated with the presence of large tumors. Cell-mediated immune reactions have also been detected against human leukemia-associated antigens. During delayed hypersensitivity studies with membrane extracts of autologous leukemia and remission WBC, positive reactions were obtained with leukemic extracts and not with extracts of remission cells. Extracts of allogeneic acute leukemia cells were found to produce positive reactions in about one-third of patients with the same type of leukemia, but were unreactive in patients with a dissimilar type of leukemia. Extracts of allogeneic remission cells and normal WBC gave negative results. Major difficulties involved with the use of assays of cell-mediated immunity for practical clinical problems include: the preparation of large standardized batches of antigenic materials, the improved characterization of antigens, the nature of effector cells in patients and controls, and conditions for augmentation of cell-mediated immunity to leukemia-associated antigens. (48 refs.)

77-0689 Liver Cancer Cell Culture Yields "Australia Antigen". (Eng.) Anonymous (No affiliation given) JAMA 237(16): 1667; 1977.

Hepatitis B surface antigen (HBsAg) was cultured from hepatoma cells from a South African man who died of liver cancer in 1973; HBsAg was detected in his blood. The antigenic material produced by the cells is similar to HBsAg derived from human plasma, and the activity of the material is neutralized by specific antiserum. Ultrastructural examination has not shown the presence of any viruslike particles in either the nucleus or cytoplasm of the cultured hepatoma cells. The nature of the association between HBsAg and primary liver cancer can now be studied in a tissue-culture system. The correlation between hepatoma and circulating HBsAg has been noted in many different countries. (no refs.)

77-0690 Interactions of Lymphocytes with Oncogenic Viruses. (Eng.) Hirsch, M. S. In: Mechanisms of Tumor Immunity. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley & Sons): pp. 287-303; 1977.

The mechanisms involved in the development of leukemias or lymphomas in mice as a result of C-type oncornavirus infection may involve virus-induced immunosuppression and selective virus-induced autoimmunity, with consequent subversion of the host's antiviral and antitumor defense mechanisms. Human B lymphocytes appear to be the major target cells for EBV, which has been implicated as a cause of infectious mononucleosis and African Burkitt's lymphoma. Lymphoblastoid cell lines derived from Burkitt's lymphomas, but not from infectious mononucleosis, show a chromosomal abnormality (8-14 translocation). This abnormality may influence the likelihood of EBV-induced transformations that lead to lymphoma development. Human cytomegalovirus may be activated from a latent state within donor WBC following blood transfusions by a graft-versus-host reaction. Two herpesviruses of subhuman primates, *Herpesvirus saimiri* (HVS) and *Herpesvirus ateles* (HVA), are not oncogenic in their species of origin but do induce lymphomas and leukemias in other subhuman primates. The lack of lymphoma development in natural hosts may be the result of more efficient immune responsiveness against virus- or tumor-associated antigens. (164 refs.)

77-0691 **Genetics of Tumor Resistance.** (Eng.) Lilly, F. (Bronx, NY) Neefe, J. *Transplant Proc* 9(1); 1301; 1977.

Genetically controlled factors for resistance to viral tumors in the mouse include both H-2-linked and H-2-independent genes. Factors not associated with H-2 include structural and regulatory genes for expression of virus and virus-specified proteins. H-2-associated factors seem to influence recovery from tumor rather than tumor induction. Presumably, they act through immunologic mechanisms controlled by immune-response genes. Restriction of cell-mediated antitumor immunologic responses to targets with H-2 homology to the responder has been observed in many systems. Susceptibility to leukemogenesis by radiation leukemia virus has been mapped to the H-2D vicinity. Fluorescent antisera to the virus show an early peak of reactivity in thymus cells in both susceptible and resistant hosts, but a late peak is seen only in susceptible mice. A different class of factors involving spontaneous leukemogenesis in AKR mice exists. Early tumor induction has been demonstrated when thymus cells cultured on monolayers of "old" thymus epithelium are transplanted to young recipients. Thymic epithelium may exert an age-dependent influence on viral leukemogenesis. (no refs.)

77-0692 **β -Microglobulin and the Major Histocompatibility Complex.** (Eng.) Peterson, P. A. (Inst. Medical and Physiological Chemistry, Biomedical Center, Univ. Uppsala, Uppsala, Sweden) Rask, L.; Ostberg, L. *Adv Cancer Res* 24: 115-163; 1977.

A review is presented of the biochemical characteristics of the major histocompatibility antigens and of related proteins, with emphasis on data pertinent to the major murine systems. The isolation and characteristics of β -microglobulin, which occurs in small amounts in body fluids such as plasma, urine, saliva, cerebrospinal fluid, and colostrum, as well as in the 17th mouse chromosome, are discussed. It has only recently been recognized that this protein is present on the surface of WBC. The function(s) of the gene products controlled by the major histocompatibility complex (MHC) is largely unknown; however, a common factor of in vivo or in vitro reactions involving these glycoproteins is beginning to emerge. The MHC region most probably arose early in evolution and, in giving rise to other genes upon duplication and diversification, may have provided the embryo for the immune system. (210 refs.)

77-0693 **Comments on the Relationships Between H-2 Antigens and Other Antigens in the Mouse, with Special Reference to Possible Implications for the Host-Tumor Systems.** (Eng.) Oth, D. (Experimental Cancerology and Radiobiology Unit, INSERM U 95, Vandoeuvre-les-Nancy, France) Meyer, G.; Berebbi, M. *Folia Biol (Praha)* 32(1): 1-18; 1977.

The relationships between the major histocompatibility (H-2) antigens and other antigens in the mouse are reviewed. Interactions between H-2 antigens and some non-H-2 antigens have been demonstrated in cytotoxicity tests mediated by T lymphocytes in vitro. In vivo cell transfer tests have yielded evidence that indicates that some non-H-2 antigens are dependent on H-2. Several possible explanations for the H-2 to non-H-2 interrelationships are discussed and placed into two categories: H-2 action at the gene level and H-2 action at the gene product level. Under gene-level action, there are three possible mechanisms: (1) the non-H-2 antigen may be the product of an H-2 mutation; (2) a non-H-2 antigen generating agent may derepress some repressed H-2 genes; and (3) H-2 may serve as a regulator gene for non-H-2-coded non-H-2 antigens. At the gene product level, non-H-2 antigens may be modified H-2 gene products; H-2 and non-H-2 antigens may be closely associated spatially, but on different molecules; or structures may be present that enable H-2 molecules to influence non-H-2 ones. In host-tumor relationships, the non-H-2 antigens are tumor-associated antigens (TAA). Many TAA do not appear to be dependent on H-2, and the different TAA on experimental tumors belong to several categories, including cross-reacting and non-cross-reacting. The inverse relationship between the amounts of H-2 and TAA antigens on the cell surface and the fact that chemical extraction does not permit distinction between H-2 antigens and TAA are suggestive of some kind of relationship between them. The H-2 haplotype has been found to play an important role in the susceptibility of mice to several oncogenic viruses. H-2 may modulate the anti-TAA response and, in some situations, it may influence the TAA and/or the immune reaction against the TAA. (83 refs.)

- 77-0694 **Chronic Lymphocytic Leukaemia as an Immunoproliferative Disorder.** (Eng.) Brouet, J. C. (No affiliation given.) Seligmann, M. *Clin Hematol* 6(1): 169-184; 1977.

The identification and classification of human lymphoid cells from chronic lymphocytic leukemia patients as B- or T-lymphocytes based on membrane markers is reviewed. The immunofluorescent detection of surface-bound membrane immunoglobulins (SIg) is the most reliable marker of B cells. When monospecific antisera to various Ig chains, subclasses, or allotypes are used, evidence of the genetic commitment of the cell is obtained. Receptors for the Fc fragment of IgG and for various proteins of the complement system are also present on the membrane of B-cells. The Fc fragment are detectable with IgG aggregates and by rosetting with RBC's sensitized by an IgG antibody. Complement receptors can be detected utilizing a method of rosette formation between lymphocytes and RBC coated with IgM antibodies. Fc and complement receptors are also found on monocytes and granulocytes and cannot be used to identify the cellular origin of proliferating cells. The most widely used membrane markers for T-derived lymphocytes are the spontaneous rosette formation with sheep RBC and the reactivity of the lymphocytes with heteroantisera raised against either thymocytes, peripheral T-cells, or human brain. Immunofluorescence testing is more satisfactory than cytotoxicity tests using heteroantisera because it allows for the simultaneous testing of other markers and the direct morphologic examination of the positive cells. (102 refs.)

- 77-0695 **Cell-mediated Reactions In Vivo.** (Eng.) McCluskey, R. T.; Bhan, A. K. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 1-25; 1977.

The heterogeneity and complexity of the cellular events occurring in cell-mediated reactions in vivo are examined. Knowledge concerning significant aspects of cell-mediated reactions (changes in draining lymph nodes, effector mechanisms, and the nature and immunologic specificity of the mononuclear cells in infiltrates) is considered in the light of experiments carried out with several types of reactions. In instances in which cell-mediated mechanisms are responsible for tumor destruction, the relative importance of macrophages, lymphocytes, or other WBC may vary widely from one tumor or allograft to another. Human cancers are frequently associated with a mononuclear cell reaction. However, the presence, intensity, and nature of the infiltrate are variable from one neoplasm to another, and many neoplasms evoke no reaction. Little attention has been devoted to the inflammatory cells directly participating in reactions that develop in and around neoplasms. Further investigations will help to elucidate the ways in which the immune system can destroy neoplasms. (105 refs.)

- 77-0696 **Human Pulmonary Macrophages in Disease and Neoplasia.** (Eng.) Golde, D. W. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 171-180; 1976.

Studies on the human lung macrophage, obtained by bronchopulmonary lavage from normal smokers and nonsmokers and patients with acute leukemia, pulmonary infiltrates, and pulmonary alveolar proteinosis, are reviewed. The pulmonary macrophages have characteristic ultrastructural features and, in cigarette smokers, "smoker inclusions" are clearly visible light and electron microscopically. Available data suggest that the human alveolar macrophage originates from bone marrow stem cells and arrives at the lung via the circulating monocyte. In addition, the macrophage has a proliferative capacity, suggesting that the lung macrophages can replenish their numbers by replication in situ and are not wholly dependent on peripheral blood monocytes. In patients with acute leukemia, the lung macrophage population is maintained through long periods of monocytopenia and cytotoxic chemotherapy. Direct evidence for a hematopoietic derivation of the alveolar macrophages in man was obtained by studies on a female patient with a successful bone marrow graft from a male donor in whom macrophages containing the Y chromosome were obtained by bronchopulmonary lavage. Alveolar macrophages from patients with acute leukemia produce substantial quantities of colony-stimulating activity, which suggests that these cells may stimulate granulopoiesis in times of need and recruit more monocytes to maintain the alveolar macrophage population for pulmonary defense. In some suspension cultures of cells obtained by bronchopulmonary lavage, substantial lymphocyte transformation was observed after the addition of phytohemagglutinin. This proliferative response was documented radioautographically by ³H-thymidine incorporation. The lung macrophages in patients with pulmonary alveolar proteinosis are morphologically and functionally defective, the most prominent defect being their inability to kill ingested *Candida pseudotropicalis*. (26 refs.)

- 77-0697 **The Macrophage as a Tumoricidal Effector Cell: A Review of in Vivo and in Vitro Studies on the Mechanism of the Activated Macrophage Nonspecific Cytotoxic Reaction.** (Eng.) Hibbs, J. B. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 83-111; 1976.

Studies on the tumoricidal effect of activated macrophages are reviewed. Normal mouse peritoneal macrophages are not tumoricidal under usual or unstressed physiologic conditions, but must be converted to tumoricidal activated macrophages by a mediator. Activated macrophages participate as cytotoxic effector cells in both nonspecific and specific tumor destruction. A major difference between the two mechanisms of tumor resistance is the source of the stimulus for lymphocytes to produce a mediator that converts normal macro-

phages into cytotoxic activated macrophages. In nonspecific tumor resistance the inducing agent is unrelated (BCG, toxoplasma, etc.); in specific tumor resistance it is an antigen specific to the tumor. The critical modification underlying the destruction of tumorigenic cells by activated macrophages may be local or general membrane destabilization in both cells, which favors focal and temporary membrane fusion. The apparent universal susceptibility of tumorigenic cells to destruction by activated macrophages suggests that decreased membrane stability may be fundamental to expression of the neoplastic phenotype. In addition to morphologic and biochemical modifications, experiments suggest that destabilization of macrophage membranes may occur in parallel with activation. Trypan blue pretreatment of peritoneal macrophages harvested from mice with chronic BCG or toxoplasma infection reduced the ability of the macrophage to destroy tumor target cells in vivo. It also suppressed the rejection of tumor allografts in mice and reversed toxoplasma- and BCG-induced nonspecific resistance to tumor growth. It is concluded that macrophages evidently have an important role in cytotoxic effector cells in host resistance to cancer. (68 refs.)

77-0698 **Tumor Macrophages in Host Immunity to Malignancies.** (Eng.) Evans, R. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 27-42; 1976.

studies on the possible involvement of macrophages associated with growing tumors in the prevention of metastatic spread and on the presence of these macrophages during tumor regression following azathioprine therapy are reviewed. In animal models, the level of macrophages, which, are of host origin, found in a given transplantable tumor is fairly constant during progressive tumor growth and from one animal passage to the next. Circumstantial evidence suggests that at the level of macrophages found in a particular tumor type may be related to the ability of that tumor to provoke an immune response, which in turn may determine the rate and frequency of tumor metastasis. In view of a recent report that latent metastatic foci may be present even with high immunogenic tumors, this evidence may need to be reconsidered. In vitro studies indicate that cytotoxic macrophages actively destroy tumor cells, but there is also evidence that normal cells are lysed by activated or immune macrophages. The possibility that macrophages inhibit DNA synthesis of dividing syngeneic lymphocytes suggests that macrophages recognize certain membrane structures of dividing cells, as well as debris and dead or damaged host cells. Little is known, however, about the mechanism of tumor cell killing, whether by direct cell to cell contact or by a soluble labile factor. The changes in cellular composition of a murine fibrosarcoma after azathioprine therapy were investigated in preliminary experiments using trypsin dispersal of tumors and histological section. The antitumor effect was noticeable on the fifth day after the beginning of treatment, and within 10 days the tumors had completely regressed. The percentage

of macrophages remained fairly constant and, since the tumor was decreasing in size, this indicates that there was no increase and probably a decrease in macrophage numbers during or after therapy. Two possibilities are suggested for a mechanism of action during rejection: (1) regression is mediated directly by azathioprine; and (2) azathioprine predisposes the tumor cells to attack by certain effector mechanisms, which might involve either macrophages and/or lymphocytes. (49 refs.)

77-0699 **Role of Macrophages in Host Defense Mechanisms.** (Eng.) Mackaness, G. B. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 3-13; 1976.

The similarities between resistance to infectious disease and resistance to tumors are reviewed in relation to the role of macrophages in host defense mechanisms. While studying the phenomenon of concomitant immunity it was discovered that all of five unselected syngeneic tumors of mice caused a profound depression of natural resistance to infection. Within 12 hr of implanting 10^5 or 10^6 tumor cells sc in the foot, host resistance to iv challenge with a sublethal dose of *L. monocytogenes* was abolished. This impairment of resistance to an infectious agent was attributed to a factor that could be detected in serum within 12 hr of implanting tumor cells in the foot. This inhibitor of host resistance must act through its ability to interfere with the activities of mononuclear phagocytes, particularly circulating monocytes, because these are the only cells directly involved in resistance to *L. monocytogenes*. A factor that could interfere with the mobilization of blood-borne cells at the site of a tumor implant would bestow on tumor cells a period of grace that would allow them time to get established in a hostile environment. The tumor-bearing host soon shows a reversal of these effects and an immunity appears that, once established, prevents further implantations of tumor cells, even though the factor with tumor-promoting and proinfective properties persists in the serum in almost undiminished concentrations. This seems to imply that specific, tumor-directed immunity may be powerful enough to overcome the tumor's inhibitory influence in innate resistance at a new implantation site, but not be strong enough to contend with excessive concentrations of an inhibitor within the primary tumor. These findings suggest that there exists an innate mechanism of resistance to neoplasia that makes use of the same cell types that operate against microorganisms. They also indicate that if this nonimmunological defense is once breached, only an acquired mechanism of resistance (specific immunity) can weight the balance in favor of the host. The existence of an innate defense against colonization of the tissues by neoplastic cells also suggests a plausible basis for the concept of immunological surveillance. It is concluded that an almost perfect parallel exists between cell-mediated antimicrobial immunity and resistance to neoplasia and that the macrophage plays a major role in defense against neoplasia. (48 refs.)

77-0700 Macrophage Activation by Lymphocyte Mediators and Tumor Immunity: A Brief Review.

(Eng.) David, J. R.; Piessens, W. F.; Churchill, W. H. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 67-80; 1976.

Studies demonstrating that macrophages activated by lymphocyte mediators have an enhanced ability to kill tumor cells are reviewed. Macrophages that have been incubated with macrophage activating factor (MAF)-rich lymphocyte supernatants or MAF-rich Sephadex fractions exhibit changes that appear to reflect alterations in the macrophage membrane, such as increased adherence to culture vessels, an increase in ruffled membrane movement, and enhancement of both the rate and extent of phagocytosis of dead mycobacteria and starch. Mediator-activator macrophages also show important functional changes, including enhanced bacteriostasis and enhanced tumoricidal capacity. The tumoricidal capacity of macrophages activated by MAF was studied in a syngeneic strain 2 guinea pig tumor system, and it was observed that macrophages activated by MAF kill syngeneic tumor cells but not normal cells. This finding is consistent with previous reports that activated macrophages obtained from mice immunized with a number of different microorganisms kill transformed cells but not their normal counterparts, whereas macrophages from nonimmunized mice kill neither cell type. Membrane alterations possibly analogous to those found between normal and transformed cells might be present between normal and activated macrophages. Such surface changes might lead activated macrophages to recognize altered tumor cell membranes, leading to interaction and subsequent killing of the tumor cell. There is an increasing amount of evidence that MAF and migration inhibitory factor (MIF) are the same. Macrophages can also be rendered cytotoxic for tumor cells by a product of activated lymphocytes called "specific macrophage arming factor" (SMAF). SMAF is a product of thymus-dependent lymphocytes stimulated by antigen and is cytophilic. It is concluded that there must be at least two different mechanisms by which normal macrophages are rendered cytotoxic for tumor cells, one by arming and one by activation. (50 refs.)

77-0701 Functional Activity of Cytolytic T Lymphocytes in the Rejection of Tumor Target Cells. (Fre.)

Brunner, K. T. (Dept. Immunology, Swiss Inst. Experimental Cancer Res.--ISREC, Ch. des Boveresses, 1066 Epalinges-sur-Lausanne, Switzerland) Cerottini, J. C. *Ann Immunol (Paris)* 128C(1/2): 473-483; 1977.

The mechanism of the cytolytic T-lymphocyte (CTL) destruction of grafts and tumors is reviewed. In addition, the characteristics of CTL memory cells, the functional activity of CTL induced in secondary mixed leukocyte cultures (MLC-2) against allogeneic tumor growth in mice, and the specificity of CTL formed in response to Moloney sarcoma virus (MSV)-induced tumors are reported. Preliminary results indicate that memory CTL appear in the spleen and

peripheral blood of mice 7 days after the ip injection of allogeneic tumor cells and persist in high concentration for at least 3 mo. The functional activity in vivo of CTL induced in MLC-2 was demonstrated by the simultaneous inoculation of irradiated (650 rads) C57BL/6 (H-2b) mice with cells from MLC-2 stimulated by spleen cells of DBA/2 (H-2d) mice and allogeneic P-815 (H-2d) tumor cells. The iv transfer of CTL induced in the MLC-2 protected the irradiated mice effectively against growth of the sc-injected allogeneic tumor cells. In demonstrating the immune-response specificity of CTL against tumors induced by MSV, highly reactive CTL were obtained from spleen cell MLC-2 provided by C57BL/6 and DBA/2 mice immune to the MSV tumors. In vitro, the CTL obtained from the two different MLC-2 lysed the syngeneic MSV-induced tumor cells preferentially. The results show a genetic restriction related to the histocompatibility complex upon induction of CTL cytotoxic activity. (39 refs.)

77-0702 Lymphocyte Chalone. (Eng.) Attallah, A. M. In: Chalones. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 355-383; 1976.

The evidence for the existence of a cell-specific, but not species-specific, and noncytotoxic endogenous inhibitor of the transformation and proliferation of lymphocytes in vitro, a chalone, is discussed. Studies on the specificity of the chalones indicate that lymphoid tissue ultrafiltrates strongly inhibit the incorporation of tritiated thymidine into the acid insoluble DNA of lymphocytes but not of bone marrow cells, diploid human fibroblasts, or HeLa cells in vitro. There is a specificity of T-derived chalones for T cells as opposed to B cells in immunologically stimulated systems. The mitotic inhibitor is in the molecular weight range of 30,000 to 50,000 daltons. The chalones appear to reside in a peptide-containing macromolecule in which neither DNA nor RNA has any specific activity. Filtration studies indicate that the chalones could travel as a less than 30,000 dalton material in close association with RNA. The results of C57BL/6 mouse studies with skin grafts indicate that lymphocyte chalones from spleens could inhibit the immunologically-produced transformation of human lymphocytes in mixed lymphocyte culture and this concentrate could inhibit the release of macrophage inhibition factor from transformed human lymphocytes in vitro. Chalones are uniquely cytotoxic to mouse and human lymphoblastic cell lines in vitro. It is proposed that chalones maintain a high level of plasma membrane adenylate cyclase activity, assuring a high intracellular concentration of cyclic AMP. Therefore, an inhibition of nucleoside kinase activity is produced limiting the DNA synthesis in diploid cells. (52 refs.)

77-0703 Genetic Resistance to Bone Marrow Transplantation and to Lymphoma-Leukemia. (Eng.) Trentin, J. J. (Div. Experimental Biology, Baylor Coll. Med.

ine, Houston, TX) Bennett, M. *Transplant Proc* 10(1): 1303-1306; 1977.

The work of eight investigators suggests that genetic resistance (GR) to normal bone marrow transplantation (BMT) is a manifestation of a natural resistance mechanism against lymphoma-leukemia in vivo and may have the same effector mechanism(s) as the spleen natural killer (NK) cell-mediated lysis of lymphoma in vitro. In one study, GR to BMT was found to be a manifestation of a lymphoma-leukemia resistance mechanism in C57 mice. ^{89}Sr abrogated both GR to BMT and GR to Friend virus leukemogenesis. Although attempts to develop an in vitro effector system for GR to BMT have been unsuccessful, several in vitro NK cell systems for rodent tumor cells have been reported. A study of the effects of several factors (with known effects on GR to BMT in vivo) on splenic NK cells directed against YAC lymphoma cells in vitro indicated that GR to BMT may be a manifestation of a natural resistance mechanism against lymphoma-leukemia. Also reported are studies of the effector cells responsible for the rejection of incompatible marrow cell allografts in irradiated mice in vivo, the F_1 antiparent cell-mediated cytotoxicity reaction in vitro, and the natural killing of tumor cells in vitro by lymphoid cells. One investigator characterized the NK cell in mice in detail and discussed the human NK cell. Another presented data on NK cells elicited in the peritoneal cavity of mice 3-10 days after ip injection of BCG organisms. A model on the GR to BMT was developed in which the number of bone marrow cells needed to protect lethally irradiated recipients in various allogeneic combinations could be determined. (no refs.)

77-0704 **Regulation of Inflammatory Responses in Neoplastic Disease.** (Eng.) Ward, P. A.; Cohen, S. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 305-313; 1977.

Two mechanisms by which the immunologically induced inflammatory response can be modulated in neoplastic disease are presented. The first involves the elaboration of specific inhibitory factors that block the activity of inflammatory mediators, such as complement-derived and lymphokine chemotactic factors. The second involves regulation of the expression of cell-mediated immunity by the lymphokines themselves. The reported defective inflammatory responses in humans and animals with malignant tumors may be due to imbalances in the control of leukotactic systems. If there are to be successful immunologic defenses against tumors, the leukotactic defects will have to be circumvented. Lymphokines can act as suppressive agents. The cellular targets of the lymphokines are likely to be immobilized, activated, or otherwise preempted systematically and thus relatively unavailable for reaction at the site of an evolving immunologic reaction. Regulation can occur either via the participation of endogenous inhibitory factors or by the spillover of excess mediators themselves into the general circulation. (24 refs.)

77-0705 **Immunologic Enhancement of Tumor Growth.** (Eng.) Hellstrom, K. E. (Hellstrom, I.) In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 147-174; 1977.

The mechanisms of immunologic enhancement that allow tumors to escape from immunologic control are discussed. There is evidence that suppressive factors exist not only in the sera of tumor-bearing individuals but also bound to lymphoid cells and that they can abrogate certain aspects of cell-mediated immune responses to tumors. Inoculation of animals with certain hyperimmune sera or certain antigen preparations from tumors can facilitate tumor growth in vivo. Free tumor antigens and antigen-antibody complexes can specifically block lymphocyte-mediated cytotoxic reactions to tumor antigens. T lymphocytes are involved in the in vitro synthesis of blocking factors by spleen cultures from tumor-bearing mice. The higher concentration of tumor antigens and of immune complexes in the area of a growing neoplasm may facilitate its escape from immunologic control. The impact of the blocking mechanism in vivo may be decreased by removal of the source of tumor antigens, passive administration of unblocking antibodies, and by the generation of effector cells that are resistant to the blocking effect. Procedures by which blocking serum activity can be decreased in vivo may be useful for tumor therapy. (132 refs.)

77-0706 **Bacterial Neuraminidase and Altered Immunological Behavior of Treated Mammalian Cells.** (Eng.) Ray, P. K. (Chittaranjan Natl Cancer Res. Centre, Calcutta, India) *Adv Appl Microbiol* 21: 227-267; 1977.

Vibrio cholerae neuraminidase (VCN) treatment of cells increases their antigenicity and immunogenicity. Normal, fetal, and malignant cells all become increasingly immunogenic after VCN treatment in vitro and in vivo. Tumors previously treated with VCN show reduced transplantability when injected into animals, and animals that are immune to VCN-treated tumor also become refractory to normal tumor challenge. A tumor vaccine prepared by VCN treatment followed by x-irradiation can immunize animals against syngeneic tumors. This indicates that perhaps secondary tumors can be treated or recurrences prevented using VCN, after the primary is removed or reduced in size by conventional therapeutic methods. The mechanism of action of the tumor vaccine is hypothesized. (337 refs.)

77-0707 **Mechanisms of Tumor Cell Destruction.** (Eng.) Henney, C. S. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley & Sons): pp. 55-86; 1977.

Four pathways by which the immune system and its products

can lead to tumor cell destruction in vitro are reviewed: (1) complement-mediated lysis following antibody activation; (2) antibody-dependent cell-mediated cytotoxicity, which is due to effector cells bearing receptors for the Fc portion of immunoglobulin G molecules; (3) T-cell-mediated lysis, which is effected by cells with a membrane-associated antigen receptor; and (4) macrophage-mediated cytotoxicity. The terminal events in cell destruction seem to be similar regardless of the pathway leading to the insertion of lesions in a target cell's membrane. Water influx through the membrane lesion leads to disordered osmotic regulation, and the resulting colloid osmotic forces cause disruption of the plasma membrane. Circumstantial evidence suggests that the lytic attack is directed against the lipid moiety of the plasma membrane. (128 refs.)

77-0708 Skin Cancer in Immunosuppressed Patients. (Eng.) Maize, J. C. (State Univ. New York at Buffalo, Sch. Medicine, Buffalo, NY) *JAMA* 237(17): 1857-1858; 1977.

The role of immunosuppression in the development of skin cancer in transplant recipients is discussed. Data from several cancer centers indicate that skin cancers in renal transplant patients occur primarily on sun-exposed skin and that most are squamous cell carcinomas rather than basal cell carcinomas. Immunosuppression may allow for the sequential progression of solar keratoses to in situ squamous cell carcinomas to invasive squamous cell carcinomas by suppressing the immunologic surveillance function of the immune system. Immunosuppressive drugs may also act as cocarcinogens with UV light in the induction of skin cancers. In a recent study, the incidence of skin cancer in renal transplant patients was 7.1 times that expected in the general population, and the frequency of squamous cell carcinoma was 36.4 times that expected. Patients subjected to long-term immunosuppression should be encouraged to wear protective clothing and to use sunscreens when exposed to sunlight. The skin should be examined at checkups, and suspicious lesions should be biopsied so that skin cancers can be diagnosed and treated at early stages. (12 refs.)

77-0709 Immunodeficiency and Cancer. (Eng.) Stutman, O. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 27-53; 1977.

The association of spontaneous or induced immunodeficiencies with increased tumor incidence in experimental animals and in man is evaluated. This association in experimental animals is apparent only in a limited number of systems (tumor development by polyoma and other DNA viruses and, perhaps, herpesvirus), and the number of exceptions to the predictions of the immune surveillance theory is high. A reflective analysis of tumor incidence in patients with primary

and secondary immunodeficiencies does not support the generality of immunologic surveillance as an operative mechanism. It suggests a more restricted possibility related especially to the development of lymphoreticular tumors. The association of increased risk for tumor development in immunodepressed patients with diseases other than those requiring organ transplantation is not well-established and needs further definition. The cause of the increased incidence of certain tumors in immunodepressed hosts is still unexplained. The orthodox interpretation of immunologic surveillance as a thymus-dependent immune mechanism capable of destroying in situ tumors is questionable. (260 refs.)

77-0710 Neoplasms of the Immune System. (Eng.) Jaffe, E. S.; Green, I. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 251-286; 1977.

The immunologic characterization of lymphoreticular malignancy and related functional studies are reviewed. Although nodular lymphoma and chronic lymphocytic leukemia are B-cell neoplasms, they appear to represent proliferations of different subclasses of B cells. Areas in which surface marker studies are particularly needed include the diffuse lymphomas, both the poorly differentiated lymphocytic and the histiocytic (or large-cell) types. Several types of functional studies have been performed on the mononuclear cells of patients with different types of lymphomas during the past yr. The studies were of two general classes. (1) peripheral blood mononuclear cells were examined in patients in whom these circulation mononuclear cells were composed of normal cells (ie, Hodgkin's disease), and (2) studies in patients whose circulating cells were malignant (ie, acute and chronic lymphatic leukemia). The functional studies in patients mirror to some extent the immunologic studies being performed by immunologists investigating the activities of normal lymphocyte populations. A combination of functional studies and immunochemically analytic studies may be fruitfully performed on cell membrane antigens of selected malignant cell populations, with the expectation of the chemical identification and isolation of tumor-specific transplantation antigens as well as the identification of the structures responsible for immunologic functions. (276 refs.)

77-0711 Cancer and the Immunity System--1977. (Eng.) Good, R. A. (Sloan-Kettering Inst. Cancer Res., New York, NY) *West J Med* 126(2): 135-137; 1977.

Experiments demonstrate that chemically induced cancer caused by physical agents or viruses, and spontaneous cancers of animals frequently possess readily identifiable antigens that are foreign to the host and can be recognized by the immunological system when it has been properly stimulated. In experimental systems, the immunologic machinery has been harnessed repeatedly to prevent, treat, or even cure

cancer, sometimes without other modalities. Some spontaneous tumors possess antigens foreign to the host, but tumor progression involving immunological selection or other escape mechanisms may render the antigens on the surface of any spontaneous cancers either very weak or nonexistent. This is the case, then the problem of developing immunotherapy or immunoprophylaxis of cancer becomes much more difficult and less susceptible to the focus of specificity. However, studies with human tumors suggest that antigens foreign to the host and characteristic of the tumor have been described. Few, if any, of the tumor antigens for human cancers have been defined sufficiently in precise, critical serological analyses. Recent work on the serology of human malignant melanoma is highlighted. (29 refs.)

77-0712 **Infantile Stress, Immune Modulation, and Disease Patterns.** (Eng.) Dutz, W. (No affiliation given) Kohout, E.; Rossipal, E.; Vessal, K. *Pathol Annu* 11: 5-454; 1976.

Evidence for the concept of persistent immune modulation and its contribution to disease prevalence is reviewed. Also, results from a study on infants with various nutritious and infectious disorders from an Iranian orphanage are reported. Low immunoglobulin (Ig)G and high IgM serum levels were characteristic for infected, malnourished and/or premature infants. Numerous studies have shown that malnutrition and stress in early life interfere with cell-mediated (T-cell) immunity. A model is proposed for a relationship between T-cell defects and the onset of neoplasia; the incidence of neoplasia along with atrophy of the cell-mediated immune system increases with age. Although this immunity plays only a small role in prevention of chemical carcinogenesis, it seems to be of great importance in the development of lymphoma and neoplasia of the upper gastrointestinal tract. Studies of the frequency and geographic prevalence of lymphomas are described. Early infantile infection appears to lead to thymic atrophy and T-cell deficiency, hyperplasia of the B-cell system due to B-cell stimulation and finally the development of B-cell lymphoma targeted to nasopharyngeal, cervical and axillary lymph nodes. Immune imbalance in both ulcerative colitis and Crohn's disease appears to favor the development of neoplasia. (252 refs.)

77-0713 **Lymphokines in Tumor Immunity.** (Eng.) Yoshida, T.; Cohen, S. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley & Sons): pp. 87-108; 1977.

Experimental studies that suggest a potentially important role for lymphokines in the defense against tumor growth are reviewed. The ability of lymphocytes from experimental animals, either bearing tumors or immunized with tumor antigens, to produce certain lymphokines, particularly migration inhibition factor (MIF) and leukocyte migration inhibition

factor (LIF), has been confirmed repeatedly. Lymphokines have also been demonstrated in human disease in vivo; eg, MIF is found in the serum of patients with various lymphoproliferative disorders. Certain lymphokines (lymphotoxins) can kill tumor cells directly. A lymphokine (possibly related to MIF) can inhibit the migration of at least one kind of tumor cell (p815 mastocytoma) without killing it. Lymphokines can destroy tumors indirectly by initiating, focusing, and amplifying inflammatory responses. These findings suggest that lymphokines might find a role as therapeutic agents. Supernatants from human lymphoid cell lines that are known to contain various lymphokine activities have been injected into mammary carcinomas. Clinical regression was seen in 16/18 lesions. These human experiments are still very preliminary and must be interpreted cautiously. (177 refs.)

77-0714 **Existence of Tumor Immunity in Man.** (Eng.) Herberman, R. B. In: *Mechanisms of Tumor Immunity*. Green, I.; Cohen, S.; McCluskey, R. T., eds. (New York: John Wiley and Sons): pp. 175-191; 1977.

The characteristics of human immune reactions, particularly their specificity, and limitations of the available data are reviewed in detail. Skin testing of tumor patients may be a very practical and reliable method for monitoring cell-mediated immunity to tumor-associated antigens. Measurement of antibodies in the sera of patients with sarcoma appears to have some value in monitoring the course of the disease. Most cancer patients react to an antigen, cancer-basic protein, which seems to be common to a variety of tumors. There are difficulties involved in testing the effects of tumor antigens on in vivo protection against tumor growth. These difficulties hinder the determination of which human tumor antigens can function as tumor-associated transplantation antigens. Since common human tumor-associated antigens have frequently been restricted to a particular histologic type of tumor, the occurrence of reactivity to organ-associated antigens needs to be examined. It is possible to postulate that some normal human reactivity is directed against antigens associated with ubiquitous viruses. Alternatively, some of the natural immune reactivity to human tumors may reflect a significant immune surveillance mechanism against tumors. (150 refs.)

77-0715 **Genetic Aspects of DNA Repair Mechanisms in Mammalian Cells.** (Eng.) Bootsma, D. In: *Fundamentals in Cancer Prevention: Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: University Park Press): pp. 397-408; 1976.

Somatic cell studies on the repair of damaged DNA in human cells are discussed. Mutants defective in DNA repair have been cultivated from patients having genetic diseases such as

xeroderma pigmentosum (XP), Cockayne's syndrome and ataxia telangiectasia (AT). Mainly as a result of the study of XP skin fibroblasts, a relationship between defective DNA repair and carcinogenesis has become apparent. The development of new, in vitro, cell-fusion techniques has allowed the formation of recombinant genomes, which can be used for complementation analysis as well as gene localization. Five different complementation groups have been detected in the excision repair-deficient XP syndrome. Although differences in DNA repair have been recognized in human fibroblast-chick RBC heterokaryons following 270 ergs/mm² UV exposure, such hybrid systems cannot be used for gene mapping. Use of a Chinese hamster-human hybrid seems more promising. Isolation, purification, and characterization of enzymes involved in mammalian DNA repair will be a prerequisite for the ultimate elucidation of the genetic basis of DNA repair. (37 refs.)

77-0716 Carcinogenic Risks Associated with Radiation. (Fre.) Latarjet, R. (Fondation Curi - Institut du Radium, 26, rue d'Ulm, 75005 Paris, France) *INSERM Symposia Series* 52: 179-190; 1976.

Several aspects of evaluating the carcinogenic risk of radiation and chemicals are reviewed: (1) effect of depletion of the ozone layer by supersonic aircraft, sulfur dioxide, and freon on the incidence of skin cancer induced by UV radiation; (2) the practical difficulties of establishing in experimental mammals and subsequently extrapolating to man a safe threshold dose of ionizing radiation; and (3) the carcinogenesis that occurs at the cellular level as a result of errors in DNA repair mechanisms. Radiation and chemical carcinogenesis produce similar DNA lesions; consequently, a quantitative unit, ie, "rad-equivalent," applicable to both types of carcinogenic activity might be established. The rad-equivalent concept for measuring carcinogenic risk may solve the complex problem of defining safe levels of exposure to carcinogenic chemicals. (14 refs.)

77-0717 Dermatoses That May Be Accompanied by Carcinoma. (Eng.) Landes, E.; Kuta, A.; Metz, B. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 2, pp. 1291-1307; 1976.

Several dermatoses that may be accompanied by carcinoma are reviewed. A critical consideration of literature cases shows that there is no psoriatic carcinoma in the true sense; it is always a secondary carcinomatosis caused by carcinogens (arsenic, x-ray, thorium X, tar, UV). In malignant degeneration of lichen planus of the skin, which is a rare occurrence, special factors, such as atrophy, pseudoepitheliomatous hyperplasia, and chronically relapsing inflammation, rather

than therapeutic measures, such as arsenic and x-ray, lead to malignant degeneration. Both squamous cell carcinoma and glossitis granulomatosa and carcinoma in candidiasis of the oral mucosa are rare. Chronic discoid lupus erythematosus (CDLE) belongs to the chronically inflammatory dermatoses, which show a considerable amount of malignant degeneration. Of the external carcinogenic factors, all the known skin carcinogens must be considered in the malignant degeneration of CDLE lesions, especially UV and x-ray; these relationships should be kept in mind when starting therapy, and any irritating local treatment should be avoided. Most observations made so far on malignant degeneration in porokeratosis mibelli (PM) can be explained by the carcinogenic effect of UV. The known biologic activity of x-ray should always be taken into account in porokeratosis lesions treated previously with irradiation. In most cases of malignant degeneration of porokeratosis, a squamous cell carcinoma developed. Malignant tumors can also occur in the terrain of acrodermatitis chronica atrophicans Herxheimer. Lichen sclerosus et atrophicus may lead to squamous cell carcinomas in both the male and female genitals, but no carcinomas have been found on the skin. In the development of carcinomas in ulcer cruris the starting point is the margin of the ulcer. The chronic inflammation and the sclerotic atrophic-hypoxic environment are of decisive significance, the marked atrophy being one of the preconditions for malignant degeneration. Malignant tumors also occur not infrequently in leprosy, particularly lepromatous leprosy. (16 refs.)

77-0718 Photoreactivation in Normal and Xeroderma Cells. (Eng.) Sutherland, B. M. In: *Fundamentals In Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: University Park Press): pp. 409-416; 1975.

Most cells contain at least three pathways for repair of DNA damaged by UV light: excision repair, postreplication repair, and photoreactivation. Fibroblasts and other cells from normal humans contain rather high levels of photoreactivating enzyme (PRE); cells from patients with xeroderma pigmentosum contain lower PRE levels. These low enzyme levels seem to be heritable, with P the dominant gene for normal PRE, and p a recessive gene for defective enzyme. All normal individuals examined in this study were either PP or Pp, and all xeroderma patients were either Pp or pp. The total resistance of an individual to the environmental burden of damage to his DNA may be evaluated by determining his total repair capacity—the sum of his capacity for excision repair, post-replication repair and photoreactivation. The development and testing of such a repair index may allow the identification of individuals with low repair capacity and thus, perhaps, of increased probability of induction of cancer. (16 refs.)

77-0719 Actinic Keratosis-Actinic Skin. (Eng.) Pinkus, H. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumport, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co): Vol. 1, pp. 437-457; 1976.

Actinic keratosis is used synonymously with solar keratosis, actinic keratosis refers to the more or less hyperkeratotic lesions on the sun-exposed skin of susceptible individuals as part of the complex of actinic skin. The lesions are classified as precancerous, because a high percentage transform into invasive squamous cell carcinoma. Biologically, they may be considered carcinoma in situ. This review covers the epidemiology and incidence of the lesions and their etiology and pathogenesis, clinical appearance, pathology, diagnosis, prognosis, and treatment. Variant forms of actinic keratosis are described, including keratosis senilis, lichen planuslike keratosis, large cell acanthoma, lentigo senilis, and disseminated superficial actinic porokeratosis. Features that distinguish actinic keratoses from inflammatory lesions, benign neoplasms, other precancerous dermatoses, and invasive skin cancer are summarized. (65 refs.)

77-0720 Bowen's Disease and Erythroplasia. (Eng.) Knox, J. M. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumport, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co): vol. 1, pp. 646-661; 1976.

Bowen's disease, an intraepidermal squamous cell carcinoma involving the skin or mucous membranes, and erythroplasia of Queyrat, Bowen's disease on the glans penis, are reviewed. Sunlight, sunlight, viruses, and trauma have all been implicated in the etiology of Bowen's disease. Eighty percent of all patients who have had Bowen's lesions excised can expect to be free for 15 yr or longer without having a recurrence. The disease can occur at almost any age and seems to appear slightly more frequently in men than women and to occur predominantly in Caucasians. Sites include the face, ears, neck, lower abdomen, lower back, buttocks, extensor aspect of the thighs and legs, and extensor aspect of the hand and fingers. Lesions are usually asymptomatic, but occasionally they are pruritic or painful. In one series of 35 patients, 28% developed a primary internal malignancy or a primary malignancy of the skin with metastasis at an average of 8.5 yr after onset of Bowen's disease. Bowen's disease has been effectively treated by surgery, by topical 5-fluorouracil in propylene glycol or cantharidin, and by radiation. Erythroplasia of Queyrat usually appears as well-defined, red, smooth, velvety plaques with little or no induration. There is a higher propensity for dermal invasion with subsequent metastasis than in Bowen's disease. Unlike Bowen's disease, there is no known increased incidence of internal malignancy and no established association with arsenic ingestion. Erythroplasia always begins on a mucosal surface but may subsequently spread to

glabrous skin. Age at the time of diagnosis varies from the third to the eighth decades. Duration of a lesion at the time of diagnosis is from several months to 25 yr. No authentic case of the disease has been reported in men circumcised in infancy. Occasionally there is mild pruritus, but pain and tenderness are absent. If the disease persists long enough, frankly invasive squamous cell carcinoma will occur. It can be treated effectively, depending on the degree of extension down the penis, by surgery, chemosurgery, topical 5-fluorouracil, or radiation preceded by circumcision. (63 refs.)

77-0721 Circumscribed Precancerous Melanosis (Dubreuilh). (Eng.) Andrade, R. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumport, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 679-702; 1976.

Circumscribed precancerous melanosis is a long-standing, slowly progressing, pigmented, very sharply outlined lesion ranging in color from pale tan to brown. It occurs equally in men and women and more frequently after middle age. Duration may be as long as 35-60 yr. Practically all cases (800) have been in Caucasians. The etiology is unknown, but the predominance of lesions on the face suggests a relationship to sun exposure. Precancerous melanosis is essentially a clinicopathologic entity having a very peculiar, distinctive clinical picture, which makes it relatively easy to differentiate from superficial malignant melanoma. In the early stage, there is a small, round or oval, tan, sepia, or brown, sharply outlined macule of 8-10 mm that progressively extends irregularly. Periods of progression may alternate with periods of quiescence and regression. Transformation into malignant melanoma occurs in 1/3 cases, at an average of 10-14 yr after onset. The histologic features are those of widespread junctional proliferation and can be interpreted only on the basis of the clinical findings. Early signs of malignant transformation include poorly outlined junction nests invading the superficial dermis, increase in the degree of cellular pleomorphism, presence of mitotic figures, invasion of the upper layers of the epidermis, and presence of an intense inflammatory reaction in the dermis. Diagnosis is based on the duration and size of the lesion, its sharp, irregular outline, its color range, and its characteristic changeability. Special attention should be paid to the differential diagnosis from the flat type of seborrheic keratosis. Grenz ray treatment in high doses is the treatment of choice. Other treatment methods include superficial destruction (electrodesiccation, curettage, electrocautery) and surgical excision. When the lesion is diagnosed and treated in time, the prognosis is good. If a malignant melanoma develops, the prognosis is better than that for a malignant melanoma developed in normal skin or in a junction nevus. (79 refs.)

77-0722 Melanoma of the Skin. (Eng.) Gumport, S. L. In: *Cancer of the Skin. Biology-Diagnosis-*

Management. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 2, pp. 950-973; 1976.

Melanoma of the skin is reviewed. True metastasizing melanomas may occur at any age but the highest incidence occurs in the fourth to sixth decades of life. It occurs at the following sites in order of frequency: lower extremity, trunk, head and neck, upper extremity, and subungual region. A good percentage of patients with melanoma give a history that would indicate the presence of a preexisting nevus at the same site. The melanoma may also arise from other lesions that contain melanocytes, such as the pigmented freckle of Hutchinson (circumscribed precancerous melanosis of Dubreuilh), the nevus pigmentosus giganticus, and possibly the benign cellular blue nevus. Superficial melanomas are those that are slow-growing, flat, completely asymptomatic, and have never bled or been ulcerated. They have a more favorable prognosis than the more aggressive invasive melanoma and may not require prophylactic regional lymph node dissection. Stage I lesions of invasive melanoma are treated by a wide and deep excision of the primary site in conjunction with selective regional lymph node dissection. In Stage II melanoma, when the lymph nodes are grossly involved with melanoma or when there are cutaneous satellites near the primary site, the prognosis for survival is less than for the Stage I melanoma. The tumor is removed even more widely than is customary for Stage I lesions, and consideration should be given to chemotherapy by perfusion at the time the regional lymph nodes are removed. Melanoma is one of a number of malignant tumors in which spontaneous regression has been documented. The occurrence of other malignancies in patients with melanoma is somewhat higher than would be expected in the general population. (93 refs.)

77-0723 The Current Rapid Increase in Incidence and Mortality from Malignant Melanoma in Developed Societies. (Eng.) Lee, J. A. (Dept. Epidemiology, Sch. Public Health and Community Medicine, Univ. Washington, Seattle, WA) *Pigm Cell* 2: 414-420; 1976.

Incidence data from cancer registries covering limited areas (counties, states) and mortality data from entire countries show the same rapid rise in malignant melanoma in prosperous white populations. This rise is selective for particular age groups. Both young men and women show a remarkable rise that carries through to middle age; there has been a decline in those 65 yr and older. The incidence of malignant melanoma of the head and neck in men has increased two times and that of the trunk three times in the last 20 yr. In women, the greatest increase has been in melanomas of the lower limb. The changes observed in hospital, registry, and mortality experience are the result of a genuine and large rise in the incidence of malignant melanoma. (24 refs.)

77-0724 Current Concepts of the Biology of Human Cutaneous Malignant Melanoma. (Eng.) Clark, H. (Dept. Pathology, Temple Univ. Medical Sch., Philadelphia, PA) Mastrangelo, M. J.; Ainsworth, A. M.; Bolognia, D.; Bellet, R. E.; Bernardino, E. A. *Adv Cancer Res* 24: 203-338; 1977.

The etiology, developmental biology, immunobiology, and ultrastructure of malignant melanoma are reviewed. The induction of melanoma may depend partly on heritable cellular susceptibilities to neoplastic transformation. There has been a significant increase of melanoma in those born since 1920. Demographic and epidemiologic data strongly indicate that sunlight plays a major role in the increasing incidence of melanoma; Sunlight may interact with other factors such as special melanocytic moles. Parameters such as levels of invasion and thickness of primary tumors permit rather accurate prediction of metastases. The cytoplasm of melanoma cells, especially the fine structures of melanosomes, is progressively altered. If "competence for metastasis" is understood at the cellular level, then a rational approach to the control of the disease may be made. (245 refs.)

77-0725 Langerhans Cells: Involvement in the Pathogenesis of Mycosis Fungoides. (Eng.) Rowd, G. (McGill Univ. Cancer Res. Unit, McIntyre Medical Sciences Building, 3655 Drummond St., Montreal, Quebec H3G 176, Canada) *Br J Dermatol* 95(6): 665-672; 1976.

Evidence is presented for a possible role of the Langerhans cells in the pathogenesis of mycosis fungoides. Allergic contact hypersensitivity experiments indicated that the Langerhans cells not only may act as the initial receptor of the allergen in the integument, but they may also be capable of transporting allergens to the local lymph nodes to initiate a primary immune response. Production in the lymph nodes of specifically sensitized lymphocytes capable of recognizing the allergens may lead to a homing of such cells to the Langerhans cells in the epidermis. Since mycosis fungoides simulates nonspecific dermatitic reactions during its early stages it may result from a chronic exposure to contact allergens. It is suggested that in the case of mycosis fungoides, as in contact allergic hypersensitivity, the Langerhans cell acts as a trap for the externally applied allergen(s). By their capacity to transport material to the lymph nodes they may initiate the primary immune response, thereby inducing the formation of specifically sensitized lymphocytes. These transformed cells then home to the sites of initial allergen fixation in the epidermis. The reactive cells are capable of infiltrating into the epidermis, eventually contacting the allergen presented on the surface of the Langerhans cells. Lymphocytotoxic mechanisms involving direct contact or secretion of diffusible lymphokines would, once initiated, lead to various degrees of specific and nonspecific damage to Langerhans cells and the surrounding keratinocytes. The concept of immune rearrangement accompanying persistent antigenic stimulation and malignancy has been suggested and may be indicated by

triad of immune complexes, anti-immunoglobulin antibodies, and selective cellular immune unresponsiveness or anergy. Preliminary studies have demonstrated such a triad in a small number of individuals with mycosis fungoides. (43 refs.)

77-0726 Current Problems in Mycosis Fungoides and Sezary Syndrome. (Eng.) Winkelmann, R. K. Depts. Dermatology and Anatomy, Mayo Medical Sch.; and Mayo Clinic and Mayo Foundation, Rochester, MN 55901) *Am J Med* 62: 251-269; 1977.

Mycosis fungoides (MF) is thought of as a chronic inflammatory and potentially prelymphomatous cutaneous syndrome that presents in three stages; the parapsoriasis, infiltration, and tumor stages. Typical MF has a protracted course, but when the tumor or ulcerative stage is reached, death usually occurs within 2 yr. MF is a polymorphous reticulosis of the skin with a mixed cellular infiltrate composed of lymphocytes, histiocytes, and occasional eosinophils, neutrophils, and giant cells. The infiltrate is characterized by a large mononuclear cell with a hyperchromatic nucleus that is found in the dermis and epidermis. There are no histopathologic criteria for determining the precise onset of MF because of the lack of specificity of the early histologic picture. Skin biopsy usually reveals the diagnostic features of MF in the infiltrative plaque stage. In the tumor stage the infiltrate is massive and usually occupies the entire dermis. Some cases display considerable cellular pleomorphism with large numbers of bizarre-appearing tumor cells. These cases may be difficult to differentiate from histiocytic lymphoma. Besides the skin, involvement may also occur in the lymph nodes, lung, spleen, liver, and kidney. Immunopathology, staging, and treatment are also discussed. Sezary syndrome is erythroderma with circulating atypical mononuclear cells. The Sezary cell is an atypical lymphocyte with a convoluted nucleus and an ample cytoplasm, often with vacuoles or pseudopods. The Sezary syndrome has four variants: pre-Sezary syndrome, Sezary syndrome, Sezary phenomenon, and T-cell leukemia. (115 refs.)

77-0727 Origin and Significance of the Basal Lamina and Some Interstitial Fibrillar Components in Epithelial Neoplasms. (Eng.) Gould, V. E. (No affiliation given) *Pathol Annu* 11: 353-386; 1976.

The origin of the concept of the basal lamina (BL) and evidence indicating that neoplastic epithelium is primarily responsible for the production of its supportive BL are reviewed. Ultrastructural studies of 240 cases of epithelial cancer indicated that some epithelial neoplasms may express reactivation of their embryonic-collagen synthetic capability. Most of the tumors examined were infiltrating ductal carcinomas of the breast, which have variable patterns of BL deposition. Basal lamina was most consistently encountered

near cells with evident myoepithelial differentiation. Well-differentiated epithelial cancers showed consistent BL deposition. Reduplicated BL were conspicuous in papillary thyroid carcinomas and in some benign epithelial tumors such as schwannomas. In all of the 15 schwannomas studied, bundles of collagen fibers exhibited abnormal periodicity. In some breast, sweat and salivary gland tumors, myoepithelial cells of ectodermal origin appeared to be responsible for the secretion of collagen and other extracellular macromolecules. Evidence suggested collagen secretion by squamous cells in three spindle cell cancers studied. BL defects or gaps may reflect focal cellular dedifferentiation and result in early carcinomatous invasion. (77 refs.)

77-0728 Reasons for Familial Aggregation in Hodgkin's Disease (Letter to Editor). (Eng.) Katin, M. J. (Roswell Park Memorial Inst., Buffalo, NY 14263) *N Engl J Med* 296(16): 940; 1977.

Comments are made on the suggestion that the increase in Hodgkin's disease among siblings of affected persons is due to interpersonal transmission of, or common exposure to, some etiologic agent. The data presented to support this conclusion cannot be considered valid, because nonrelated persons living in the same household, such as adopted siblings, were not used as controls. The genetic origin of Hodgkin's disease cannot be overlooked. The hypothesis that the critical period for exposure is probably before 20 yr of age cannot be accepted as an explanation of why no spouse pairs were identified without an analysis of age at the time of marriage. (no refs.)

77-0729 Reasons for Familial Aggregation in Hodgkin's Disease (Letter to Editor). (Eng.) Grufferman, S. (Duke Univ. Medical Center, Durham, NC 27706) Cole, P.; Smith, P.; Lukes, R. J. *N Engl J Med* 296(16): 941; 1977.

Arguments are presented supporting the view that the familial aggregation of Hodgkin's disease does not have a genetic basis. The sex concordance of excess risk, for both sexes, is not consistent with known patterns of gene transmission. The absolute risk for siblings of affected persons is low, only about 3%, even when the relative risk is high, 5% to 9%. There have been only three reported cases with more than two affected siblings in a family, unlike other neoplasms that are known or suspected to be genetic. Hodgkin's disease does not belong to any of the known cancer family syndromes. The study was too small to seek possible genetic markers and to evaluate the prevalence among spouses of affected persons. (no refs.)

77-0730 Genetic, Familial, and Environmental Factors in Childhood Cancer. (Eng.) Meadows, A. T. *In:*

Trends in Childhood Cancer. Donaldson, M. N.; Seydel, H. G., eds. (New York: John Wiley and Sons): pp. 15-22; 1976.

Factors in childhood cancer are assessed. Lymphomas and leukemia may be induced in experimental animals by viral agents. Burkitt's lymphoma, occurring in school-age African children in a tropical environment in which malaria is endemic, is uniformly associated with a specific pattern of antibodies to Epstein-Barr virus. Ionizing radiation has been known to be associated with an increased rate of cancer, especially leukemia. Synthetic estrogens, such as stilbestrol, have been linked with vaginal carcinomas in young girls whose mothers receive those drugs during pregnancy. Site-specific tumors may aggregate in families. Neoplasia-associated syndromes in children include the immune-deficiency diseases, xeroderma pigmentosum, Fanconi's anemia, Bloom's syndrome, and neurofibromatosis. The prototype of the hereditary childhood neoplasms is retinoblastoma. The continued intimate collaboration of the clinician, the epidemiologist, and the basic scientist, professionals with different approaches, can define associations of etiologic significance. (40 refs.)

77-0731 Productivity in Normal and Leukemic Granulocytopoiesis. (Eng.) Fliedner, T. M.; Hoelzer, D.; Steinbach, K. H. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects.* Neth, R.; Gallo, L. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): pp. 185-194; 1976.

Concepts of normal and leukemic cell proliferation and differentiation are presented, using granulocyte kinetics as a model. In normal efficient granulocyte production, the characteristic blood granulocyte concentration appears to be the result of a feed-back controlled cell-renewal system which is capable of life-long granulocyte production and adapting itself to increased demands. Granulocyte production is drastically altered in both chronic and acute myelocytic leukemia. Myelocytes in chronic myelocytic leukemia (CML) divide $3-4 \times$ as compared with $2 \times$ in normal marrow, and the size of the total myelocyte mass in CML patients is estimated to be $3-25 \times$ normal. Increased myelocyte proliferation as well as an increased stem cell input are postulated to contribute to the expansion in granulocytopoiesis seen in CML. In acute myelocytic leukemia (AML), the blood picture is characterized by the presence of some mature granulocytes and blast cells. Usually, the blast cells in the bone marrow show a low ^3H -thymidine labeling index as compared with normal myeloblasts or promyelocytes when exposed to ^3H -thymidine in vitro or in vivo. If leukemic blast cells are labeled in vitro with ^3H -cytidine and autotransfused, the calculated blood transit times are between 3.7 and 8.5 days, much longer than those of granulocytes. Studies of the fate of leukemic blast cells appear to have the potential to differentiate into granulocytic precursors and to mature into granulocytes. Thus, the accumulation of blast cells in human AML may indicate the

extreme of inefficiency, i.e., the bulk of cells accumulates in the form of blast cells which may have the potential for differentiation and granulocyte production, but rarely do so in full-blown acute leukemia. In various forms of acute leukemia, the labeling pattern of blood granulocytes is markedly different from the normal pattern in the following respect: the labeling indices never reach normal values and are below 30% (not exceeding 10-20% in many cases); the labeled cells disappear quite rapidly so that after 6 days many or all have disappeared; in other cases, a few may be seen until 12 days after ^3H -thymidine injection. The deficiency of granulocyte production in acute leukemia appears to be a consequence of a highly ineffective cell proliferation and differentiation in the appropriate precursor compartments and points to the stem cell pool as the major site of leukemic cell transformation (35 refs.)

77-0732 Immunological Aspects of Diagnosis and Pathogenesis of Lymphogranulomatosis. (Rus.) Iarlan, A. A. (No affiliation given) *Med Radiol (Mosk)* 21(10): 18-22; 1976.

The status of cellular immunity in the etiology of Hodgkin's disease is reviewed. Patients with Hodgkin's disease have decreased numbers of T-cells in blood. Percent of blasts in cultured lymphocytes stimulated with phytohemagglutinin (PHA) was 76.4% with cells from healthy subjects, 37.6% with patients in Stages I-II, 18.2% with patients in Stage III and 0-10% with patients in Stage IV. Immediately after radio- or chemotherapy, functional activity of T-cells was depressed; during remission the depressed levels showed partial recovery. (no refs.)

77-0733 Preleukemic Syndrome. (Ita.) Ascari, E. (Istituto di Clinica Medica Generale e Terapie Mediche "Adolfo Ferrara," Università degli Studi, Pavia, Italy) *Minerva Med* 68(6): 393-395; 1977.

The preleukemic stage is defined as specific but variable hematologic and bone marrow alterations that precede the appearance of a nonlymphoid acute leukemia. The frequency of the preleukemic syndrome is estimated at 4%-31%. The interval between the hematologic alterations and the appearance of the acute leukemia is usually short, 1 yr in half the patients and about 2 yr in over three-fourths. The preleukemic syndrome appears to be more frequent in aged individuals and in men and is clinically characterized by asthenia and anemia. The most frequent hematologic signs are macrocytic anemia with anisopoikilocytosis, neutropenia, and thrombocytopenia. Bone marrow alterations are mainly characterized by hypercellularity, massive erythroblastic hyperplasia with megaloblastic or sideroblastic elements, granuloblastic hyperplasia, and megakaryocytic morphological alterations (14 refs.)

77-0734 Primary and Secondary Granule Contents and Bactericidal Capability of Neutrophils in Acute Leukaemia. A Commentary. (Eng.) Lehrer, R. I. Dept. Medicine, Center Health Sciences, Univ. California, Los Angeles, CA 90024) *Blood Cells* 2(3): 553-556; 1976.

A commentary is presented on the paper by H. Odeberg, T. Lofsson and I. Olsson appearing in the same issue and characterizing the neutrophil subpopulation of the granulocytes in patients with acute granulocytic leukemia or acute myelomonocytic leukemia. The results on phagocytosis are suggestive of impaired function by leukemic cells, but they are obscured by the day-to-day variability in this assay among cells from normal subjects. The multiple abnormalities in the metabolism, function and composition of the cells makes it difficult to deduce a specific cause for the microbicidal defect observed. It is not possible to draw any conclusions on the intracellular role of the chymotrypsin-like cationic proteins from studies on two deficient patients. Extensive comments on possible functions of lactoferrin in the neutrophils are included. (16 refs.)

77-0735 Ultrastructure of Malignant Lymphomas. (Ger.) Schaefer, H. E. (Pathologisches Institut der Universitat, Cologne, W. Germany) *Haematol Bluttransfus* 18: 49-61; 1976.

Electron microscopic cytomorphological findings in various malignant lymphomas are presented, and the related literature is reviewed. Reed-Sternberg cells are currently considered lymphocytic in origin, as transformed lymphocytes or normal lymphoblasts. A highly pronounced proliferation of bundled filaments, measuring about 80 Å, was observed in lymphoma cells, especially in plasma cell leukemia. The usual genesis of ribosome-granular material complexes found in various types of lymphomas remains to be ascertained. Tubular crystals were found in only one case of chronic, apparently leukemic lymphocytosis in man. Tubuloreticular structures, found in nonneoplastic blood lymphocytes, lymphoma cells, and in various animal tumors, may be the result of a special cytoplasmic reaction to an unknown, perhaps viral factor. The presence of immunoglobulin crystals in blood lymphocytes in chronic lymphadenosis is an indication of altered immunoglobulin synthesis. (51 refs.)

77-0736 Factors in the Pathomechanism of Chronic Lymphocytic Leukemia. (Eng.) Theml, H. (Erste Medizinische Abteilung des Städtischen Krankenhauses München-Schwabing, Munich, W. Germany) *Love, Begemann, H. Annu Rev Med* 28: 131-141; 1977.

A review is presented of recent data that characterize the pathogenetic cells in chronic lymphocytic leukemia (CLL)

and aspects of their production and turnover. CLL is characterized by an accumulation of highly differentiated lymphocytic cells that have the structural and metabolic characteristics of a neoplastic cell line of B lymphocytes (except in cases of "T-cell CLL"). However, they lack the immunoglobulin-secreting ability of normal B cells, and are immunologically incompetent and inert. There is a decreased population of normal B cells and, occasionally, a slightly increased T-cell population. The increased population of pathological cells is attributable to a tenfold increase in cell proliferation rate and a fivefold increase in their life span. There also is a disturbance of exchange of cells between the intra- and extravascular pools. These characteristics clarify the development of the clinical picture: through packing of the bone marrow and spleen with pathological cells, anemia, thrombocytopenia, and finally granulocytopenia develop. The gradual displacement of normal B cells results in extreme hypogammaglobulinemia as the main component of a multifactorial syndrome of immune deficiency. (65 refs.)

77-0737 Ribonucleic Acids in Normal Lymphocytes and in Those from Patients with Chronic Lymphatic Leukemia (Literature Review). (Rus.) Blinov, M. N. (Leningrad Inst. Hematology and Blood Transfusion, Leningrad, USSR) *Probl Gematol Pereliv Krovi* 21(11): 35-38; 1976.

Literature pertaining to the biosynthesis and metabolism of RNA in normal lymphocytes and in those from patients with chronic lymphocytic leukemia (CCL) is reviewed. The overall RNA content in the CLL lymphocytes was approx 20% less than that in normal lymphocytes. Light RNA (4S-10S) amounted to 40% of the total RNA in normal lymphocytes and to only 0.5% of the total in leukemic lymphocytes. Incorporation of labeled precursors into RNA was significantly higher in the leukemic lymphocytes. (55 refs.)

77-0738 Some Problems of Leukemogenesis and the Tasks in the Search for Antileukemic Preparations Under Experimental Conditions. (Rus.) Reshchikov, V. P. (Lab. Experimental Therapy Leukemia, Central Inst. Hematology and Blood Transfusion of USSR Ministry Public Health, Moscow, USSR) *Egorov, L. V.; Khanykina, O. K. Probl Gematol Pereliv Krovi* 21(10): 11-16; 1976.

Leukemogenesis and the development of antileukemic preparations were reviewed. The study indicated the following: that the development of tumors and leukemia in the organism cannot be regarded as an autonomic process; that the synthesis of antileukemic preparations should be performed along with investigations on the interrelationship between the chemical structure and the biological action of the preparation; and that antileukemic preparations may be found

among the inhibitors of enzymatic processes and among the natural hemopoiesis regulators. (31 refs.)

- 77-0739 Remarks on Locomotion of Normal and Neoplastic White Blood Cells in the Organism.** (Eng.) Strauli, P. (Div. Cancer Res., Inst. Pathology, Univ. Zurich, Birchstrasse 95, CH-8050 Zurich, Switzerland) *Blood Cells* 2(3): 467-471; 1976.

The evidence for locomotion of normal and neoplastic cells in the body is reviewed. While a few experimental models permit direct visualization and cinematographic recording of cell locomotion in vivo, the evidence presented is histological, and therefore indirect. Leukemia cells are excellent candidates for locomotive activity. A great deal is known about the movement of lymphocytes. Movement of myeloid cells, including granulocytes, occurs in the local inflammatory response. While random movement of white cells cannot be excluded, an attempt is made to interpret locomotion as a reaction to a certain environmental constellation. The ecosystem acting upon cellular locomotion is different for lymphocytes (excitaxis) and granulocytes (chemotaxis). The coordination of patterns of migration requires regulation at various levels, the most important one being responsiveness of cells to homeostatic signals. (32 refs.)

- 77-0740 Treatment of Idiopathic Thrombocytopenic Purpura (ITP).** (Eng.) Ahn, Y. S. (Center Blood Diseases, Dept. Internal Medicine, Univ. Miami Sch. Medicine, Miami, FL 33152) Harrington, W. J. *Annu Rev Med* 28: 299-309; 1977.

The treatment of idiopathic thrombocytopenic purpura (ITP) consists of general and specific measures. The general treatment includes antipyretics to reduce fever, the treatment of infections, the correction of azotemia, and treatment with prednisone to bring about improvement in bleeding tendency. Alcohol and drugs that handicap platelet formation should be avoided. The specific treatments include splenectomy, glucocorticoid administration, and treatment with immunosuppressants. Splenectomy yields an overall permanent remission rate of 70%-80%. Splenectomy is usually successful in patients under 45 yr of age who have less-severe cases of the nonautoimmune forms of ITP and who have shown prior response to glucocorticoids. The initial effects of glucocorticoids on platelet levels probably represent handicaps imposed on the reticuloendothelial macrophages. Steroids are indicated in patients in whom splenectomy is contraindicated. Glucocorticoid therapy is not satisfactory for long-range management and may actually perpetuate thrombocytopenia in some patients. The most frequently used immunosuppressants are azathioprine, cyclophosphamide, and the vinca alkaloids. These agents affect multiple aspects of the immune system, including macrophage function. With the exception

of the vinca alkaloids, prolonged periods of treatment are required before response is observed. Due to the carcinogenic and teratogenic potential of nonsteroidal immunosuppressive agents, they should not be used as the primary modality of therapy and they should be avoided in children and in women of childbearing age. (74 refs.)

- 77-0741 Mucin Histochemistry of the Colon.** (Eng.) Filipe, M. I. (No affiliation given) *Curr Top Pathol* 63: 143-178; 1976.

The amount and histochemical characteristics of the mucin secreted by carcinomas of the large intestine are variable. In most cases, secretion is scanty or absent. The few goblet cells are either empty or they contain a little mucus as a drop near the luminal border or, more often, as a narrow ring around an otherwise empty theca. In papillary tumors, it is common to find villi covered by goblet cells that contain sulfated mucin side by side with others in which sialomucin predominates. In well-differentiated adenocarcinomas, one frequently observes a mixture of neutral and acid nonsulfated mucins in the glandlike lumens. Mucoid carcinomas are more common in the right colon than the left. Sialomucins generally form the bulk of these tumors but differ from those in the normal goblet cell by their greater susceptibility to sialidase digestion. Mucous secretion is variable from case to case and in different areas of the same tumor, so that in most adenocarcinomas of the large intestine, both types of acid mucin will be found. There is a predominance of sialomucin secretion in what appears to be normal mucosa in ulcerative colitis who have developed carcinoma, but rarely in those without at least early malignant change. This transitional mucosa can frequently be suspected, as dilatation and branching of crypts lined by tall goblet cells are accompanied by secretion that is largely sialomucins. Likewise, it is found around and mingling with carcinoma and frank precancer. A villous pattern of mucosa may be seen in normal healing of ulcers, repeated in ulcerative colitis, and precancer. Recognition that there are three different forms of villous mucosa is significant, because overemphasis of villosity can lead to overdiagnosis of precancer. Mucin changes may add another dimension in the diagnosis of precancer. (157 refs.)

- 77-0742 Histologic Classification of Gastric Polyps.** (Eng.) Elster, K. (No affiliation given) *Curr Top Pathol* 63: 77-93; 1976.

The size and shape of gastric polyps are significant with regard to the technical problems of therapeutic procedures. For example, the stalked polyp may be removed by snare during endoscopy and will not pose any problems, whereas the large broad-based polypoid lesion has to be treated surgically. A grouping of colon polyps according to their pathogenesis has proved suitable for the study of malignant transformation and this should also be tried for gastric polypoid lesions. I

necessary to separate hyperplasia from true neoplasia, which means that the hyperplastic polypoid lesion must be differentiated from benign epithelial growths of the gastric mucosa. Classification of the histologic structure and cellular origin should also include the nonepithelial polyps. However, the connective tissue of the gastric mucosa has no special features, and gastric polyps of this kind can be excluded. An exception in regard to mesenchymal polyps is the inflammatory fibroid polyp. It is only seen in the stomach and is a connective tissue nonneoplastic process. When epithelial polyps, independent of their hyperplastic or neoplastic origin, are defined as proliferation of gastric mucosal epithelium, the type of epithelium and its ontogenesis have to be considered for classification. The manifold structure of the gastric mucosa depends not only on the different topography of the cardia, fundic, antral, and pyloric mucosa, but also on the different mucosal layers. The tissue of origin of a polyp can be surface epithelium, the glandular neck (foveolar) region, gastric glands, or combinations of several types of epithelium. The theoretical basis for histologic classification is applied to foveolar hyperplasia, the hyperplasiogenous polyp, adenomas, proliferation with cellular atypia, and gastric dysplasia. (23 refs.)

77-0743 Primary Liver Carcinoma and Liver Cirrhosis. (Eng.) Shikata, T. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 53-71; 1976.

The incidence of liver cirrhosis varies significantly from country to country, as evidenced by mortality rates ranging from 3 to 35/100,000 of the general population. The geographic distribution of cirrhosis suggests variation of the etiologic relationship between cirrhosis and hepatocellular carcinoma (HCC), since the latter is uncommon in Europe and the US. The liver pathology of 220 patients with HCC was analyzed upon necropsy at the University of Tokyo in the period 1940-1972. Nine cases were associated with less common types of liver cirrhosis; 181 of the remaining 211 cases were associated with the common types of cirrhosis, and 17 were associated with hepatic fibrosis. Only 13 cases had an remarkable liver pathology in areas not involved by the cirrhosis. It is hypothesized that in acute and in active stages of chronic active hepatitis, hepatitis B (HB) antigen-containing hepatocytes and perhaps hepatitis virus are removed immunologically. Persistent, long-term infection of hepatitis virus may be associated with an immunodeficient state against HB surface antigen or other HB virus-associated antigens. Thus, hepatitis virus or HB surface antigen-containing cells cannot be removed by the usual mechanisms of cellular immunity. HB surface antigen-containing cells are often most numerous in noncancerous portions of the liver with HCC. On the other hand, frequency of antibody to HB surface antigen is very low in patients with HCC who do not have HB surface antigen. Although HCC occurs most often

in HB surface antigen-positive macronodular cirrhosis, it sometimes develops in other types of cirrhosis. (49 refs.)

77-0744 Precancerous Liver Cell Populations and Their Identification. (Eng.) Farber, E.; Hartman, S. P.; Solt, D.; Cameron, R. In: *Fundamentals in Cancer Prevention: Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 71-87; 1976.

Characteristics of hepatocarcinogen-induced preneoplastic lesions and their role in cellular evolution are reviewed. At least four new hepatocyte populations may be cell precursors in carcinogenesis: (1) hepatocytes in enzyme-deficient, glycogen-storing foci or islands that seem to show disturbances in iron metabolism and a hypertrophied smooth endoplasmic reticulum; (2) early hyperplastic nodules containing hepatocytes arranged in two-cell-thick (or more) plates and showing many of the same changes (they may undergo maturation, remodeling or differentiation, during which one-cell-thick plates are formed); (3) late hyperplastic nodules, which are similar to the early nodules but do not seem to become remodeled or do so very slowly (with time, they show an increase in malignant hepatocytes); (4) areas of hyperbasophilic hepatocytes, which seem to be the ultimate precursors for some liver cancers. These foci show decreased RNase and DNase activities and accelerated RNA and DNA synthesis. Some positive markers that may be indicative of carcinogenesis or associated with the new cell populations include preneoplastic antigen, α -fetoprotein, selective isozymes, and γ -glutamyl transpeptidase. The possibility of selective cytotoxicity occurring in hepatocyte populations is discussed. This approach, which suggests that resistant islands of cells are induced by carcinogens, may be utilized to study altered cell populations in vivo and measure an end point to carcinogenesis. (69 refs.)

77-0745 Florid Oral Papillomatosis. (Eng.) Wolff, K. In: *Cancer of the Skin. Biology-Diagnosis-Management*. Andrade, R.; Gumpert, S. L.; Popkin, G. L.; Rees, T. D., eds. (Philadelphia: W. B. Saunders Co.): vol. 1, pp. 797-813; 1976.

Florid oral papillomatosis, a proliferative papillomatous hyperplasia of the oral cavity, is reviewed. This disorder is characterized by a slow progression and a tendency to recur; it may transform into carcinoma. Florid oral papillomatosis is a rare disorder; details of 11 cases from the literature and 8 patients seen by the authors are tabulated. There appears to be a preponderance of men among those affected. All but two of the patients were over 55 when they developed the first symptoms. All cases were Caucasians, and there was no geo-

graphic prevalence. Florid oral papillomatosis represents a precancerous condition, but it is not clear whether it is benign initially, requiring a carcinogenic stimulus to transform into carcinoma, or whether it harbors malignant potential ab initio. A viral etiology has been implicated, but no cogent evidence yet exists for this assumption. The chronic, persistent irritations exerted by dentures may be more significant, and tobacco may also be a precipitating factor. The most common sites of involvement are the buccal mucosae, the upper and lower molar gingivae, and the floor of the mouth. Initially the lesions are superficial, but as the process continues there is considerable infiltration of the tissue. The lesions are asymptomatic. Frank carcinoma does eventually supervene, but clinically it is difficult to assess the onset of the malignant change. Metastases have not been described. The most striking and prominent histologic feature is the benign appearance of the lesions, which contrast with the impression gained by clinical inspection. The lesions can be removed by surgical excision, but this does not prevent the development of new growth in other areas of the mucous membrane. Nevertheless, wide surgical excision and grafting appear to be superior to all the other measures tried so far (curettage, electrodesiccation, electrocautery, x-ray). Chemotherapy appears to be the most promising approach for the future. The prognosis is assumed to be much better than that of verrucous carcinoma, but many more cases will have to be observed before a definite conclusion can be reached. (51 refs.)

- 77-0746 **Genetics of Retinoblastoma.** (Eng.) Kitchin, F. D. In: *Tumors of the Eye. Third Edition.* Reese, A. B., ed. (Hagerstown, MD: Medical Dept., Harper & Row): pp. 125-132; 1976.

The human genetics of retinoblastoma (RB) are reviewed. Estimates of the incidence of RB range from 1:15,000 to 1:30,000 live births. The prevalence of the disease has increased slightly in recent years due to improved diagnosis and treatment; previously, victims did not survive to the reproductive years. Pedigree studies infer an autosomal dominant mode of expression, especially in those with bilaterally affected parents. There is a wide range in penetrance (2p), however, ranging from 2p = 86.1% in those with bilaterally affected parents to 40.9% in those with carrier parents. Because of the lethality of RB, a large, noninherited, sporadic mutational component is involved, especially in unilateral RB cases. As a group, RB cases show no consistent chromosomal anomalies. Conversely, however, in one chromosomal defect syndrome, Dq- (a small deletion in one of the D group chromosomes, most probably number 13), over half of the cases have RB. Genetic counselling may, in most cases, determine the risk of RB in the offspring of parents affected with familial or sporadic RB. (79 refs.)

- 77-0747 **Electron Microscopy of Tumors of the Eye and Ocular Adnexa.** (Eng.) Font, R. L. In: *Tumors*

of the Eye. Third Edition. Reese, A. B., ed. (Hagerstown, MD: Medical Dept., Harper & Row): pp. 351-386; 1976.

Illustrations are presented demonstrating the utility of electron microscopy (EM) in establishing the histologic diagnosis of various eye tumors that may be misdiagnosed or diagnosed with difficulty using light microscopy (LM). In one case, a large cell with acidophilic cytoplasm, previously diagnosed as a ganglion cell by LM, was correctly identified as a rhabdomyoblast after the detection of actin and myosin bundles under EM. A distinction between alveolar soft part sarcoma and rhabdomyosarcoma may be made by the EM detection of PAS-positive, diastase-resistant crystalline inclusions. EM examination can also differentiate between intraocular melanophages and melanoma cells. The identification of an argentaffin-staining carcinoid cell showed an additional advantage of EM to more easily determine the source of metastatic lesions to the eye. Thus, EM is a valuable aid in the investigation of ocular tumor pathology. (93 refs.)

- 77-0748 **Benign Bone Tumors Associated with Visceral Tumors. Pathogenetic and Nosological Hypotheses.** (Fre.) Caron-Poitreau, C. (Departement de Radiologie, C.H.U. Saint-Louis-Lariboisiere, 75010 Paris, France). Laval-Jeantet, M.; Katz, M. *J Radiol Electrol Med Nuc.* 57(8/9): 625-628; 1976.

The pathogenesis and classification of benign bone tumors associated with visceral tumors is reviewed. The Mafucci's and perhaps 10 million pounds per yr are utilized in fabrics and plastics. (multiple chondromas and angiomas usually located in the limbs) and the Gardner's syndrome (osteomas, colon polyposis, and soft tissue fibromatous and lipofibromatous tumors) are well-defined and of genetic origin. A variation of the syndromes includes endocrine tumors, often of the ovary. Multiple tumors of bone and viscera are considered to be of embryonal tissue origin. The concept of the hamartoma (proliferation of embryonal tissue of high potential for differentiation) and the bone-visceral tumor syndrome in relationship to this concept are discussed. (15 refs.)

- 77-0749 **Systemic Angioendotheliomatosis: A Possible Disorder of a Circulating Angiogenic Factor.** (Eng.) Person, J. R. (Mayo Clinic, 200 First St. SW, Rochester, MN 55901) *Br J Dermatol* 96(3): 329-331; 1977.

Reported cases of angioendotheliomatosis are briefly reviewed. In eight cases in which this disease was fatal, autopsy revealed the involvement of the kidneys, CNS, or skin in five; the heart or lungs in four; and the gastrointestinal tract or reticuloendothelial system in three cases. The angiogenic aberration in systemic angioendotheliomatosis may be the result of a circulating angiogenic factor. A substance of this type would account for the intravascular location and multicentricity of this disease. The circulating angiogenic factor

may be produced by a diffuse vascular insult such as endocarditis or a well-vascularized tumor. In the cases in which autopsy was performed, two patients were found to have small, seemingly unrelated tumors, two had hepatic hemangiomas, one had a renal leiomyoma, and one had a cavernous hemangioma of the liver and a fibrotic tumor of the renal medulla. (19 refs.)

77-0750 **Myeloma and Other Paraproteinemias.** (Eng.) Bonnet, J. D. (Scott White Clinic, Temple, TX 76701) *Postgrad Med* 61(2): 216-220; 1977.

The types of myeloma most likely to be seen in clinical practice are immunoglobulin G (IgG) myeloma, IgA myeloma, and Bence Jones myeloma. Diagnosis is based on a combination of major and minor criteria. The major criteria are plasmacytoma demonstrable by tissue biopsy, bone marrow plasmacytosis with 30% plasma cells, and a monoclonal globulin spike on electrophoresis of > 3.5 g/deciliter (dl) for serum IgG, 2.0 g/dl for serum IgA, or 1.0 g/24 hr for urine light chains. The minor criteria are bone marrow plasmacytosis with 10%-30% plasma cells, monoclonal globulin spike at less than above, lytic bone lesions, and serum Ig values less than 50 mg/dl for IgM, 100 mg/dl for IgA, and 600 mg/dl for IgG. Anemia indicates a poor prognosis. Hypercalcemia is an unfavorable sign with IgG myeloma but not with IgA myeloma. Azotemia is unfavorable with IgG myeloma, IgA myeloma, and light-chain disease. The presence of a large number of lytic bone lesions is considered serious if the patient is confined to bed, in which case hypercalcemia will become more severe, nausea and vomiting will occur, and dehydration will ensue. Hypoalbuminemia seems to be a negative factor. Patients with Waldenstrom's macroglobulinemia have a monoclonal spike of IgM. On histologic examination, the cells in the marrow have a more lymphoid appearance than do the plasma cells in myeloma. Lymphadenopathy and hepatosplenomegaly are permanent features. Heavy-chain disease is relatively rare. Only approx 60 cases of the α type, 30 cases of the γ type, and 7 cases of the δ type have been reported. Whether benign monoclonal gammopathies become malignant is debatable. The paraproteinemias are best characterized by the type of Ig moiety (paraprotein) produced. (8 refs.)

77-0751 **Somatostatinoma.** (Eng.) Unger, R. H. (Dallas Veterans Admin. Hosp., Univ. Texas Southwestern Medical Sch., Dallas, TX 75235) *N Engl J Med* 296(17): 998-1000; 1977.

The physiological role of the pancreatic D cell and the possible consequences of somatostatin excess in somatostatinoma are discussed. Because the somatostatin-containing D cells are located between the glucagon-secreting A cells and the insulin-secreting B cells, it was proposed that the D cells influence the mixture of insulin and glucagon that emerges

from the islet. The facts that somatostatin secretion is stimulated by the same nutrients that stimulate insulin secretion and that physiologic doses of somatostatin inhibit the entry of xylose from the gut suggest that pancreatic somatostatin may have endocrine functions involving nutrient homeostasis. In a recently reported case of somatostatinoma, the clinical picture of the patient included hyperglycemia, hypoinsulinemia, reduced body wt, anemia, and gallbladder disease. After resection of the somatostatinoma, the hyperglycemia remitted, which suggests a causal relation between the hyper-somatostatinemia and the patient's diabetes. Increased levels of somatostatin may inhibit gallbladder contraction, leading to bile stasis and increased stone formation. Hypersomatostatinemia may cause loss of appetite by diminishing the patient's appetite. (16 refs.)

77-0752 **Prostatic Adenoma and Carcinoma in Cell Culture and Heterotransplantation.** (Eng.) Schroder, F. H. In: *Prostatic Disease, Proceedings of the American-European Symposium Held in Vienna, Nov. 3-5, 1975*. Physicians Associated for Continuing Education in cooperation with The Johns Hopkins University, The University of Vienna, The University of Innsbruck. (Vienna): pp. 301-312; 1976.

Recent research in tissue culture and heterotransplantation of human prostatic tumors is discussed. Primary cultures of epithelial cells grown on serum-supplemented media, with/without hormone additions, were morphologically distinct from prostatic carcinoma cells but microscopically of the central and peripheral nervous system. These clones, which are distinct from each other. Time course studies revealed that the epithelial outgrowths originated from metaplastic benign epithelium of the prostatic acine and not from prostatic cancer cells. A transformed, metaplastic prostatic epithelial cell line, EB 33, grew slower in cultures lacking the hormone dihydrotestosterone, or when transplanted into castrated "nude" mice. The "nude mouse", an immunoincompetent strain lacking T lymphocytes, was rated a good subject for heterotransplantation of human prostatic tissue. Growth of EB 33 in castrated "nude mice" supplemented with $10 \mu\text{g}$ dihydrotestosterone/day was significantly faster than in castrated mice not given the hormone ($p < 0.05$). The development of standardized transplant techniques may lead to a reproducible model for study of the endocrine dependence of human prostatic tumors. (29 refs.)

77-0753 **Etiology of Testicular Tumors.** (Eng.) Hogan, J. M. In: *Testicular Tumors*. Johnson, D. E., ed. (Flushing, NY: Medical Examination Publishing Co., Inc.): pp. 31-36; 1976.

Evidence has been offered in support of the hypothesis that testicular tumors arise from primordial germ cells. There are

few established oncological factors responsible for testicular tumorigenesis. Although environmental, occupational, genetic, traumatic, vascular and viral influences, occurring separately or in various combinations, have been implicated, their carcinogenicity has been difficult to demonstrate. The mechanisms responsible remain largely unknown. However, it is significant that most germinal testicular tumors occur during the age of greatest sexual activity. The relationship between trauma and testicular tumors has long been recognized. However, clinical studies suggest that trauma plays no direct role in the etiology of testicular neoplasms. The occasional development of a testicular malignancy in an atrophic testis has suggested a potential etiological relationship between the two. There is no doubt that the incidence of tumors in patients with cryptorchidism is higher than in those with normally descended testes. It is recommended that: orchidopexy be performed prior to age 6 yr but not after age 10 yr, strong consideration be given to performing an orchiectomy in patients with unilateral cryptorchidism diagnosed after the age of 10 yr, and careful periodic examinations of both scrotal compartments be performed after orchiectomy or orchidopexy. (no refs.)

- 77-0754 Non-Germinal Tumors: Interstitial Cell Tumors and Tumors of Specialized Gonadal Stromal Origin.** (Eng.) Davis, W. D. In: *Testicular Tumors*. Johnson, D. E., ed. (Flushing, NY: Medical Examination Publishing Co., Inc.): pp. 229-233; 1976.

Interstitial-cell tumors are composed of cells derived from primordial mesenchyme lying within the testicular interstitial tissue. These tumors are uncommon, although they are the most frequently encountered nongerminial testicular tumors. There are two distinct age maxima, 5-10 and 30-35 yr, and one minimum, 15-20 yr. Interstitial-cell tumors in children produce a sexual precocity that can be indistinguishable from virilizing adrenal hyperplasia. The child undergoes a rapid somatic growth that is most marked in muscle development and enlargement of the penis. In adults, endocrine manifestations are variable and may be completely absent. The most common presenting symptom is gynecomastia, usually associated with a decrease in the libido or overt impotence. Hyperpigmentation of the areolae, testicular and prostatic atrophy, and loss of body hair may also be seen. Initial treatment for an interstitial-cell tumor is identical to that for other testicular neoplasms--inguinal orchiectomy, with high ligation of the spermatic cord at the internal inguinal ring. A small number of testicular tumors believed to arise from primitive gonadal mesenchyme and capable of reproducing all the features of the supporting gonadal tissue of both sexes has been reported. These tumors, termed specialized gonadal stroma tumors, comprise approx 0.4% of testicular neoplasms. The presenting symptom in most patients has been a slowly enlarging testicular mass, occasionally associated with pain. (no refs.)

- 77-0755 Epidemiology.** (Eng.) Johnson, D. E. In: *Testicular Tumors*. Johnson, D. E., ed. (Flushing, NY: Medical Examination Publishing Co., Inc.): pp. 37-46; 1976.

Testicular tumors comprise 1%-2% of all malignant neoplasms in men. Germinal tumors constitute approx 97% of all primary testicular tumors, with the remaining 3% comprised of nongerminial neoplasms. The majority of germinal testicular tumors arise in men 15-44 yr of age. Seminomas tend to develop later than other histologic types; with an average incidence from 30.7 to 41.9 yr. Testicular tumors occur infrequently in Negroes, especially those < 45 yr of age. There seems to be a slight but definite predilection toward the right side. The most common bilateral testicular tumor is malignant lymphoma, accounting for around 50% of the cases, followed by seminoma. After one testicle is removed due to malignancy, the possibility of the remaining testicle becoming malignant is 700 times greater than that in the general population. A familial tendency for testicular tumor formation has been recorded on rare occasions. At present there is no evidence to suggest that the actual incidence of these tumors is increased in twins. Most investigators currently agree that trauma bears no relationship to testicular malignancy, except as a circumstance leading to the discovery of the lesion. Metastases from testicular tumors may occur by direct extension; the bloodstream; or through the lymphatic system. Direct extension to the scrotum or spermatic tunics is rare and carries a grave prognosis. Most tumors metastasize by way of the lymphatics, except for choriocarcinoma which is notorious for its hematogenic spread. (no refs.)

- 77-0756 Cancer of the Endometrium: Diagnosis and Histogenesis.** (Eng.) Gusberg, S. B.; Frick, H. C. In: *Corscaden's Gynecologic Cancer. Fourth Edition*. (Huntington, New York: Robert E. Krieger Publishing Co.): pp. 358-403; 1977.

This chapter comprehensively reviews tumors of the corpus uteri (body of the uterus) comprising the endometrium and myometrium. Attention is concentrated on endometrial adenocarcinoma, which comprises 90% of all endometrial neoplasias. The incidence and epidemiology are examined both from a historical and a current standpoint. The etiological model of hormonal-dependent adenomatous hyperplasia is covered. Diagnostic procedures are summarized and pathologic features are illustrated. The metastatic characteristics of the tumor are also described. (no refs.)

- 77-0757 Cancer of the Endometrium: Classification and Treatment.** (Eng.) Gusberg, S. B.; Frick, H. C. In: *Corscaden's Gynecologic Cancer. Fourth Edition*. (Huntington, New York: Robert E. Krieger Publishing Co.): pp. 404-469; 1977.

The clinical aspects of tumors of the corpus uteri (body of the uterus) comprising the endometrium and myometrium are reviewed comprehensively. Preventive measures in women with recurrent bleeding or with high risk characteristics are considered first. In cases of diagnosed endometrial cancer, prognoses are given based on descriptions of clinical staging. The treatment modes of surgery and internal and external irradiation are examined independently and in combination for their curative or palliative efficacies. Shorter descriptions follow concerning adenoacanthomas and rarer neoplasms of the endometrium. (375 refs.)

77-0758 Steroid Receptor Proteins and Regulation of Growth in Mammary Tumors. (Eng.) Bruchovsky, N. (No affiliation given) Van Doorn, E. *Recent Results Cancer Res* 57: 121-142; 1976.

The regulation of mammary tissue growth by steroid hormones and relevant experimental results obtained with two animal model systems, the rat ventral prostate gland and the androgen-dependent Shionogi mouse mammary tumor, are discussed. In some hormone-resistant tumors, the resistance may result from lack of entry of the hormone into the nucleus, which seems to correlate with a lack of cytoplasmic steroid receptor protein. In others, the interaction of hormone with chromatin is probably abnormal. This interaction may control three growth responses: (1) initiation of DNA synthesis and cell proliferation; (2) the switching-off of DNA synthesis when a tissue reaches normal size (negative feedback); and (3) autophagia. The expression of these responses may be partly or totally deficient in tumors. (28 refs.)

77-0759 Canine Mammary Gland Tumors. (Eng.) Harvey, H. J. (Dept. Surgery, Animal Medical Center, 510 E. 62nd St., New York, NY 10021) Gilbertson, S. R. *Vet Clin North Am* 7(1): 213-219; 1977.

A review is presented of the epidemiology, etiology, biological behavior, tumor morphology and therapy of canine mammary tumors (CMT). Among domestic animals, the dog has the highest incidence of mammary cancer. Despite its frequency, there is little conclusive information available about CMT from well-designed prospective studies. Few facts are known about their clinical behavior and there is no universally accepted system of determining histologic type. The epidemiology of CMT has not been sufficiently studied; the etiological role of hormones in naturally occurring CMT is speculative. CMT immunology is in its infancy, as are the methods of therapy. Surgery is currently the most effective therapy. (32 refs.)

77-0760 Cancer in U.S. Non-Whites. (Eng.) Anonymous (No affiliation given) *Lancet* 1(8007): 379; 1977.

A brief report is given of an atlas for cancer mortality in United States nonwhites (blacks, American Indians, Chinese, and Japanese). High rates for liver and biliary cancer in the Western states reflect the higher proportion in this area of American Indians who are prone to these diseases. Like the Japanese, the Chinese population, primarily resident in the far West, shows high rates of gastric carcinoma. The Chinese also demonstrate a high incidence of nasopharyngeal carcinoma. Interpretation of some patterns is difficult because many areas have no nonwhites at all, and the combined influences of race and geography are hard to disentangle. Cancer rates in the black population have outstripped those in whites, and there are factors in the present environment that are absent in African countries. The atlas will aid in determining the cause of the black cancer predominance. (9 refs.)

77-0761 Primary Cancer Control in Relation to Community and Individual Responsibility. (Eng.) Higginson, J. (International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon, France) *Cancer Forum* 9: 154-164; 1976.

Primary cancer control in relation to individual and community responsibility is discussed. Human cancers can be separated into two major categories according to their suspected etiology. The first group represents those tumors for which there is strong epidemiological evidence as to cause, notably, cultural habits and occupation. For the second group, exogenous or environmental factors represent the most rational interpretation of available epidemiological data, even though the stimuli concerned have not been identified. Approx 60% of those cancers for which the etiology has not been identified are likely related to environmental factors, of which the most important component may be diet. Since it is impossible to define a completely safe dose for a carcinogen, the concept of a socially acceptable risk has been the subject of discussion. The major cancers of immediate concern are dependent on stimuli that have been present in the environment for several decades and for which there are both experimental and epidemiological data. For the control of compounds that have not yet, or have very recently, entered the environment, estimation of cancer risk and evaluation of control methods depend on studies in experimental animals, which have definite limitations. In promulgating legislation, it is desirable to distinguish between risks that can be presented in substantive terms based on available studies in man and risks that can only be guessed or estimated, since dose levels cannot be extrapolated from animals to man. In the immediate future, the greatest benefits will depend on personal action. (40 refs.)

77-0762 The Role of Epidemiology in Evaluating Potential Toxicological Hazards for Man. (Eng.) Higginson, J. In: *The Prediction of Chronic Toxicity from Short*

Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975. Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. 17, pp. 104-112; 1976.

The role of epidemiological studies in determining the risk to man of cancer from environmental sources is discussed briefly. The following topics are considered: problems with the extrapolation of the results of animal studies to man; the role of exogenous factors in human cancer; the role of epidemiology in identifying environmental hazards, determining acceptable exposure levels of carcinogens, and assessing the contribution of host factors to cancer susceptibility; the integration of laboratory and epidemiological studies; difficulties inherent to epidemiological studies on cancer, including long latent periods, low levels of exposure, and the possibility of multifactorial origin; the application of epidemiological techniques to investigating environmental carcinogenic hazards; and the role of the International Agency for Research on Cancer in cancer epidemiology. (20 refs.)

- 77-0763 Chemical Carcinogenesis and Mutagenesis: Introduction to Symposium III.** (Eng.) Rall, D. P. *In: The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. 17, p. 103; 1976.

The purpose of the symposium held by the European Society of Toxicology in Montpellier, France, June 1975, is defined to be the exploration of toxicity-testing methods with respect to carcinogenicity and mutagenicity. Toxicologists must be able to identify compounds that are capable of causing cancer or mutation in man. There are four levels at which such chemicals can be identified: Level I, molecular structure/biological activity correlations; Level II, short-term tests for mutagenesis or transforming ability; Level III, animal tests; Level IV, epidemiological studies. (no refs.)

- 77-0764 Concluding Remarks on Gene Expression and Cell Cycle Control.** (Eng.) Leffert, H. *In: Onco-Developmental Gene Expression. Papers Presented at a Conference Sponsored by the International Research Group for Carcinoembryonic Proteins, and Held at San Diego, May 29-June 1, 1976.* International Research Group for Carcinoembryonic Proteins. (San Diego, California): pp. 89-90; 1976.

Dietary intake is a potent modifier of the loss of proliferation control. In choline-deficient rats exposed to chemical carcinogens, altered endocrine patterns that mimic changes observed during liver regeneration induced by partial hepatectomy are observed. Therefore, lipotrope-deficient conditions may reregulate steady-state tissue metabolism so as to either

enhance initiation and/or progression of carcinogenesis. Purines such as hypoxanthine and inosine are also known to be involved in the promotion of DNA synthesis as shown by studies in cultured hepatocytes. A highly phosphorylated ^3H -hypoxanthine-derived, adenine-containing compound has been identified as a possible regulatory nucleotide in rat liver. Changes in the rates of proliferative transitions have been shown to be dependent on a number of internal regulatory mechanisms. Increased transport of nuclear RNA into the cytoplasm occurs during hepatic regeneration, G0 and G1 to S transitions. Involvement of phosphorylated, nonhistone chromosomal proteins has been suggested as a requisite for S-phase transcription of histone genes; nuclear protein kinases may perform these processes. DNA polymerases α and β may be directly involved in the initiation. (no refs.)

- 77-0765 Concluding Remarks on Gene Expression in Carcinogenesis and Experimental Injury.** (Eng.) Smuckler, E. A. *In: Onco-Developmental Gene Expression.* Fishman, W. H.; Sell, S., eds. (New York: Academic Press, Inc.): p. 281; 1976.

Problems encountered in studying the etiology of neoplastic transformation, along with the search for diagnostic markers, are discussed. The many so-called specific markers have all corresponded to normal components of cell development expressed at abnormal times. Studies of carcinogenesis have used many agents administered by several routes whose effects were examined at various times. The appearance of α -fetoprotein (AFP) falls into the group of "non-markers" that are the end result of altered gene expression. Liver function in relation to AFP production and host responses to injury are considered. (no refs.)

- 77-0766 Cytogenetic Aspects of Malignant Transformation.** (Eng.) Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex, England) *Exp Biol Med* 6: 1-171; 1976.

The factors that cause aneuploidy in cancer cells and the relationship between chromosomal aberrations and the neoplastic properties of the cells are reviewed. The karyotypes of neoplastic cells, agents causing chromosome damage in somatic cells, constitutional chromosome anomalies and chromosome instability associated with susceptibility to neoplasia, acquired aneuploid clones in nonmalignant and premalignant conditions, chromosomes in the leukemias and in solid tumors, neoplastic conditions of the reticuloendothelial system, tumors of the alimentary tract and of the breast and female genital tract, double-minute chromatin bodies, neoplasias of animals and plants, and in vitro techniques in the study of malignancy are discussed. Damage caused by oncogenic agents at certain chromosomal sites is directly

related to the acquisition of neoplastic properties, this damage often being manifested in the form of the chromosomal abnormalities seen in the neoplastic cells. A number of different specific numerical or structural chromosome changes are found in neoplastic cells that vary with the inducing agent. An understanding of the importance of the changes gives promise of providing an insight into the events that transform the normal cell into the cancer cell. (791 refs.)

77-0767 **The Nature of Cancer.** (Eng.) Gusberg, S. B.; Frick, H. C. In: *Corscaden's Gynecologic Cancer*. 4th ed. (Huntington, NY: Robert E. Krieger Publishing Co.): pp. 603-619; 1977.

A general review is presented of certain aspects of cancer biology. The sites of origin of tumor cells (embryonal, foreign, or normal cells), characteristics of normal and neoplastic cells, normal development, carcinogens (mechanical and chemical irritation, steroids, radiation, and viruses), and the role of heredity in susceptibility to cancer are discussed. Gynecological cancers constitute one fourth of all cancers; the present survival rate in these cancers is about 40%. (87 refs.)

77-0768 **5'-Cap of Low Molecular Weight and Messenger RNA--Its Importance in Approaches to Comparisons of Tumor and Nontumor Cell Function.** (Eng.) Busch, H.; Henning, D.; Hirsch, F. W.; Rao, M. S.; Ro-Choi, T. S.; Spohn, H.; Wu, B. C. In: *Control Mechanisms in Cancer*. *Progress in Cancer Research Therapy*. Criss, W. E.; Ono, T.; Sabine, J. R., eds. (New York: Raven Press): Vol 1, pp. 241-267; 1976.

Viral messenger RNA (mRNA), the mRNA of eukaryotic cells, and low molecular wt (MW) RNA species all contain unique 5'-Cap regions that may be important for control of cell division and for understanding the fidelity of translational systems in protein synthesis. The 5'-Cap consists of nucleotides facing in opposite directions, whereas in the RNA chain all the nucleotides face in one direction. Studies on bacterial products indicate that the sequences at the 5' end of mRNA are complementary to the sequences at the 3' end of low MW ribosomal RNA (rRNA). Juxtaposition of the Cap may be catalyzed by an enzyme or protein that approximates the 5' end of mRNA to corresponding end of rRNA. A comparison of the products produced by normal liver and Novikoff hepatomas in a wheat germ translational system demonstrated that a number of low MW proteins present in the tumor samples were missing from the samples of normal liver. On the other hand, normal liver produced products that were absent from the hepatomas. The tumor proteins comigrated with a number of proteins of the 40S and 60S subunits.

The tumor transcripts appeared to lack repressor or modulator proteins that control nuclear activity in normal tissue. (120 refs.)

77-0769 **Cell Surface Carbohydrates Revealed by Peroxidase Coupled Lectins.** (Eng.) Huet, C. In: *Immunoenzymatic Techniques. Proceedings of the First International Symposium on Immunoenzymatic Techniques, held in Paris, 2-4 April, 1975*. Feldmann, G.; Druet, P.; Bignon, J.; Avrameas, S., eds. (New York: American Elsevier Publishing Co.): pp. 493-499; 1976.

The cell surface carbohydrates revealed by the concanavalin A (Con A)-peroxidase method were investigated. Studies with normal hamster embryo cells and simian virus 40-transformed cells (Cl₈TSV₁) showed that the former bound more lectin. The Con A/peroxidase ration was 7.7 for transformed cells and 3.3 for normal cells. The normal cells were covered with a continuous dense stained material, but the transformed cells exhibited a patchy distribution of staining. Experiments in which cells were postincubated at 37 C after enzyme-lectin treatment showed that some labeled material had penetrated inside the normal cell, and the surface membrane became devoid of any staining reaction. This penetration was faster with transformed cells: most of the Con A-peroxidase-labeled material disappeared from the surface within 15-30 min, but in normal cultures it took 30-60 min. Kinetic studies revealed that 80%-95% of the peroxidase and only 10% of the lectin were released from the cell surface when the labeled cells were reincubated at 37 C. It was mostly the Con A traced by peroxidase that was released. The lectin and the enzyme were shed as a complex or concomitantly. There were two main components labeled by Con A and peroxidase: one had a short period (6-16 min) and another had a longer one (1.3-3.0 hr). When cells were postincubated at 37 C after a lectin treatment, secondary binding forces occurred between the lectin and cell surface components that rendered the lectin unavailable for inhibiting sugars. The tetrameric form of Con A was predominant at 37 C but dissociated into dimers as the temperature was lowered. Although the dimer did not induce agglutination at low temperatures, even when the incubation time was prolonged, electron microscopic studies demonstrated that it could bind free exogenous glycoproteins. It is suggested that the effects of temperature on surface membrane receptor sites and on agglutination cannot be interpreted exclusively in terms of cell surface properties. (15 refs.)

77-0770 **Membrane Anomalies of Neoplastic Cells.** (Eng.) Wallach, D. F. (Tufts-New England Medical Center, Radiobiology Div., 171 Harrison Ave., Boston, MA 02111) *Med Hypoth* 2(6): 241-256; 1976.

The membrane anomalies of tumor cells may be due to the

insertion of new material into cellular membranes. This material has been proposed to be a neolipid, but such substances have proved to be either normal lipids present in unusual amounts or lipids synthesized by embryonic cells. Extensive immunological evidence indicates that new proteins (tumor-specific transplantation antigens) occur in at least the plasma membranes of tumor cells. Many neoplastic cells lack one or more high molecular wt plasma glycoproteins, possibly due to an abnormal release of proteases that act upon the external surfaces of the membrane. The release of diverse hydrolases might modify or eliminate plasma membrane binding sites (carbohydrate or protein) for extracellular membrane ligands. Limited experimentation documents significant deviations of the membrane phospholipid composition in some tumor cells. The most impressive anomalies are observed in mitochondria, and they include high sphingomyelin levels and discrepant proportions of acidic phosphatides. The phospholipid anomalies could alter the properties of protomers or of hypothetical lipid domains separating diverse protomers. Tumor cells frequently exhibit varying glycolipid compositions. Cholesterol biosynthesis is usually inadequately regulated in tumor cells, whose cytoplasmic membranes may exhibit abnormally high cholesterol/phospholipid ratios. It appears that cholesterol is not a constitutive element of membrane protein-lipid protomers, but forms part of the lipid separating the protomers. It is proposed that the concerted behavior of tumor cell membranes might deviate from normal due to a change in the steady-state of membrane ligands, the proportion of phospholipid, the proportion of cholesterol, the proportion of glycolipid, existing proteins or lipids, or new protein inser-

tion. Anomalies responsible for abnormal membrane transport, hydrolytic enzyme release, and aerobic lactate production may affect malignancy. (122 refs.)

77-0771 Why Do Tumor Cells Have a High Aerobic Glycolysis? (Eng.) Racker, E. (Section Biochemistry, Molecular Cell Biology, Cornell Univ., Ithaca, NY 14853) *J Cell Physiol* 89(4): 697-700; 1976.

In Ehrlich ascites cells and several other tumors, high aerobic glycolysis is maintained by generation of ADP and Pi by the plasma membrane $\text{Na}^+ \text{K}^+$ ATPase. The high ATPase activity is caused by a defective pump that operates at a low efficiency. In a study of the mechanism of the Ca^{++} pump from sarcoplasmic reticulum, it has been hypothesized that ATPase acts as an energy transformer and the proteolipid as a Ca^{++} channel. If the $\text{Na}^+ \text{K}^+$ pump operates by a similar mechanism, either an excess or a deficiency of proteolipid could be responsible for the low $\text{Rb}^+/\text{lactic acid}$ ratio observed in the tumor cells. Alternatively, the lesion could be caused by a defective transformer or channel. It is possible that this high aerobic glycolysis has an influence on tumor growth. The intracellular acidity caused by glycolysis could change its metabolism because of the dependency of enzyme-catalyzed reactions on pH as well as allosteric control mechanisms. The increased glycolysis may also affect the adenine nucleotide concentrations and properties of the membrane. (16 refs.)

CHEMICAL CARCINOGENESIS

77-0772 Induced Reactivation of UV-Damaged Phage λ in *E. coli* K12 Host Cells Treated with Aflatoxin B₁ Metabolites. (Eng.) Sarasin, A. (Dept. Biological Sciences, Stanford Univ., Stanford, CA 94305) Goze, A.; Devoret, R.; Moule, Y. *Mutat Res* 42(2): 205-213; 1977.

Metabolites of aflatoxin B₁ (MAB) were prepared by incubation with the 9,000 g supernatant of the livers of rats previously treated with sodium phenobarbital plus an NADPH-generating medium. MAB promoted the reactivation of phage λ damaged by radiation, in *Escherichia coli* K12 cell lines. The reactivation process was found to be error prone: 25% of the phage DNA lesions were repaired, but mutagenesis, scored as clear plaque formation, increased as much as tenfold. Such reactivation of UV-damaged phage λ , which occurred in wild-type and in *uvrA* but not in *recA* bacteria, was inducible: phage reactivation was obtained even after a long delay following treatment of the host by MAB. This induced reactivation of UV-damaged phage in hosts treated with MAB is similar to direct or indirect UV reactivation. MAB-induced phage produced induced phage reactivation as well as prophage λ induction in lysogens and cell filamentation in nonlysogens. These cellular events were also triggered by DNA lesions caused by UV radiation and result from the induction of a metabolic pathway (the previously described SOS functions). It is postulated that, in eukaryotes, carcinogens may induce SOS functions similar to those in *E. coli*. (29 refs.)

77-0773 Histochemical Manifestations of Early and Late Changes Induced by Aflatoxin in Rats. (Eng.) Dutu, R. (Dept. Morphology, Oncological Inst., Bd. 1 Mai, 11, Bucharest, Romania) *Acta Histochem (Jena)* 57(1): 34-43; 1976.

The histochemical manifestations of late and early changes induced by aflatoxin B₁ (5 and 7 mg/kg, ip) in Wistar rats were studied. In the first group (5 mg/kg), there was an alteration of the liver carbohydrate metabolism, as shown by the reduction of polysaccharides content (acid and neutral mucopolysaccharides) and lactic dehydrogenase activity; a slight change in the Krebs cycle as shown by a reduction in NADH₂-tetrazolium reductase activity; and a change in lipid metabolism. In the second group (7 mg/kg), there was again an alteration of the liver carbohydrate metabolism marked by a decrease of neutral and acid mucopolysaccharides, predominantly in the central lobe, a decrease of lactic dehydrogenase and ethanol dehydrogenase activities, and a modification of pentose shunt metabolism; these were accompanied by a modification of the Krebs cycle enzymes, protein

metabolism, and lipid metabolism. The liver lesions after 86 and 96 wk consisted of large areas of parenchymal cells containing large droplets of fat, with loss of acid and neutral mucopolysaccharides. Particular liver parenchyma alterations were evident in animals reinjected with aflatoxin 92 wk after the first administration. They were characterized by nodules developing degenerative cytoplasmic changes. There was a tendency for regenerating areas to arise at the periphery of these nodules in relation to scattered regions of fibrosis. In the lung and intestine, there were no histological, histochemical, or histoenzymological alterations. The mesenteric lymph nodes of animals from the first group showed a decreased cortical area, the appearance of tingible bodies in germinal centers (day 7), and dilation of the subcapsular and medullary sinuses. The alterations in animals from the second group consisted of blast cells in the paracortical area (day 5), hyperactivity of the paracortical area (day 8), and a decreased cortical area. The results suggest that liver changes are dependent on dose and duration of exposure and may be detected histochemically before significant morphological changes appear. (21 refs.)

77-0774 Development of Resistance to Cytotoxicity During Aflatoxin Carcinogenesis. (Eng.) Judah, D. J. (MRC Toxicology Unit, Woodmansterne Rd., Carshalton, Surrey SM5 4EF, England) Legg, R. F.; Neal, G. E. *Nature* 265(5592): 343-345; 1977.

The relationship between the development of resistance to cytotoxicity and carcinogenesis was investigated using the mycotoxin aflatoxin B₁. Feeding young adult male Fischer rats a diet containing a low concentration (4-5 ppm) of aflatoxin B₁ for 6 wk, followed by return to the control diet, resulted in a 100% incidence of hepatocarcinoma. During the first 3 wk, histological examination of the liver indicated an acutely toxic response that resulted in the death of a considerable proportion of the hepatocytes at the end of the third week. The second 3-wk period, during which the carcinogenic response was initiated, was accompanied by a proliferation of parenchymal and nonparenchymal cells and recovery of nucleic acid synthesis. This indicates that these cells have a mechanism that makes them resistant to the acutely toxic but not the carcinogenic actions of aflatoxin. The resistance of the liver cells to the toxic action of aflatoxin B₁ was also examined in vitro. Hepatocytes were isolated and subsequently cultured from livers of control animals (BL8) and livers of animals that had received the aflatoxin-contaminated diet (BL7) for 6 wk. The cells appeared morphologically similar, but when they were treated with aflatoxin, the BL7 cells survived but the BL8 cells became structurally disorganized and detached from the dish. Rapidly dividing epithelial cell lines

were established from each of the original maintenance cultures, and the sensitivity of the cells to aflatoxin B₁ was again determined after several passages. Resistance of the original hepatocytes in the case of the aflatoxin-fed rats was still present in the cell lines derived from them. These results demonstrate that the resistance to the acutely toxic action of aflatoxin B₁, once established in the cells, is stable. (9 refs.)

77-0775 A Dose-Response Study on Urethane Carcinogenesis in Rats and Mice. (Eng.) Schmahl, D. (Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany) Port, R.; Wahrendorf, J. *Int J Cancer* 19(1): 77-80; 1977.

Diethyldicarbonate (DEC) is used for the preservation of soft drinks in Germany. Small amounts of urethane are formed from DEC. The carcinogenic effect of urethane was studied. Sprague-Dawley rats and NMRI mice were treated with urethane in the drinking water for 2 yr. In both species the daily doses were: 100, 500, 2,500, and 12,500 µg/kg. The frequency of animals with malignancies increased steadily with increasing doses, beginning at 500 µg/kg/day for rats, and 100 µg/kg/day for mice. To evaluate the possible cancer risk for man due to urethane in beverages, the observed response rates were used to extrapolate responses at lower doses. At a daily dose of 0.14 µg/kg/day (corresponding to daily consumption of a beverage with 10 ppb urethane by a 70-kg man) the upper risk limits were estimated to be 3.2 in 100,000 for rats, and 470 in 100,000 for mice (modified Mantel-Bryan procedure). Since treatment of beverages with diethyldicarbonate leads to the formation of urethane, and since a cancer risk to man from urethane cannot be excluded, replacement of DEC by a toxicologically unobjectionable compound is needed. (22 refs.)

77-0776 DNA Repair Synthesis in Guinea Pig Pancreas Following Exposure to Nitrosomethylurethane. (Eng.) Iqbal, Z. M.; Epstein, S. S. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975.* Walker, E. A.; Bogovski, P.; Gričute, L.; Davis, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 411-424; 1976.

A report is presented of the effects of the alkylating pancreatic carcinogen, nitrosomethylurethane (NMUT), on normal and repair DNA synthesis in guinea pig pancreas in vivo and in pancreatic slices in vitro. Following in vivo treatment with 30 mg/kg NMUT, a twofold increase in the incorporation of tritiated thymidine (TdR) into DNA was seen in the duodenal segment of the pancreas after 4 days. This increase in TdR incorporation probably represented in vivo DNA repair synthesis. Normal DNA synthesis in the slices was

markedly suppressed by 10 mM hydroxyurea. Considerable DNA repair synthesis took place in slices from the duodenal segment following exposure to NMUT: after 30 min of exposure to 20 mM NMUT, incorporation of TdR in the presence of 10 mM hydroxyurea was 149.3 disintegrations/min (dpm)/µg DNA, compared to 33.8 dpm/µg DNA in untreated slices. Caffeine did not inhibit NMUT-induced DNA repair synthesis in the pancreatic slices. (38 refs.)

77-0777 Intrachromosomal Distribution of Chromatid Aberrations Induced by N-Methyl-N-nitrosourethane in *Triticum durum* DESF. (Eng.) Nicoloff, H. (Inst. Genetics, BAN, Sofia 13, Bulgaria) Georgiev, S. *Mutat Res* 42(3): 453-456; 1977.

The qualitative and quantitative aspects of N-methyl-N-nitrosourethane (MNU) induction of intrachromosomal aberrations in *Triticum durum* were discussed. Presoaked seeds of *Triticum durum* were treated for 90 min at 24° with 6.8×10^{-3} M MNU at pH 4.5, and the metaphases of the first posttreatment mitosis were scored. Structural alterations were mainly of the chromatid type, including isochromatid breaks, deletion duplication, and chromatid translocation. The aberration max usually occurred after a 20-hr recovery, with 110 defects in 83 cells counted, or a metaphase aberration of 42.3%. Preferential regional localization was noted. A significant number of breaks and interchanges occurred at the terminal regions and in the centromeres, with the terminal-specific type predominating. It is not known whether this selectivity is heterochromatin-dependent. (14 refs.)

77-0778 The Carcinogenicity of N-nitroso Compounds Formed Endogenously in Mice from Ben-zimidazole Carbamate Pesticides. (Eng.) Borzsonyi, M. (Natl. Inst. Hygiene, Budapest, Hungary) Pinter, A. *Neoplasma* 24(1): 119-122; 1977.

The oncogenic effect of N-nitroso compounds formed in vivo from the pesticides Benlate and Carben-dazim when combined with sodium nitrite was studied. Swiss mice (5-6 wk old) were given 600 mg/kg Benlate or 600 mg/kg Carben-dazim (1/20 LD₅₀) twice weekly intragastrically. Drinking water containing 500 mg/liter sodium nitrite was given ad libitum. Benlate-treated mice developed lymphosarcomas in 7/30 cases. Lymphosarcomas developed in 10/30 Carben-dazim-treated mice. Electron micrographs revealed A-type virus particles in the cytoplasm of proliferating lymphoblasts. In contrast, only 4/100 control mice developed tumors. Commercially available pesticides under appropriate conditions increase tumor frequency in mice, indicating a need for more research in this area. (17 refs.)

77-0779 Cytogenetic Characteristics of Lung Tumors Induced in BALB/c Mice by Transplacental Action of N-Nitrosoethylureas. (Eng.) Likhachev, A. Y. (Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, Ministry Health USSR, Leningrad, USSR) *Bull Exp Biol Med* 82(7): 1063-1065; 1976.

The cytogenetic characteristics of lung tumors arising in the offspring of the first generation of BALB/c mice receiving a single ip injection of N-nitrosoethylurea (NEU: 20 mg/kg) on the 17th-18th days of pregnancy were used. Eleven mice were studied, but metaphase plates of satisfactory quality were obtained from only 4 mice. These four tumors were adenocarcinomas with a papillary structure. The mice bearing these tumors were killed on days 327, 329, 342, and 351 of postnatal life, respectively. A total of 145 metaphases was analyzed. The modal class was formed by cells with 40 chromosomes. Moreover, these cells with a diploid set of chromosomes accounted for > 835 of the total number of metaphases studied. In all four tumors, cells of this type were found with the same frequency. Hyperdiploid cells were observed much less often. Single metaphases consisting of 41-44 chromosomes were noted, but most cells contained 41 chromosomes. Three metaphases were tetraploid or near tetraploid. Hypodiploidy also was found in some cells, and in this case the commonest numbers of chromosomes in these metaphases were 38 and 39. Cells containing 31, 34, and 37 chromosomes were observed in different tumors. The chromosomes in all the cells had the usual telocentric structure. The study demonstrates that all tumors have a diploid set of chromosomes with a modal class of 40 and with slight variations toward hyper- and hypodiploidy. (10 refs.)

77-0780 Repair of DNA Damaged by Alkylating Carcinogens is Defective in Xeroderma Pigmentosum-derived Fibroblasts. (Eng.) Goth-Goldstein, R. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143) *Nature* 267(5606): 81-82; 1977.

Xeroderma pigmentosum (XP)-derived fibroblasts and normal human fibroblasts were treated with N-methyl-N-nitrosourea (MNU) and N-ethyl-N-nitrosourea (ENU). The amount of alkylation products formed and the rate at which they were eliminated were measured to determine if the DNA damage caused by the chemical carcinogens was repaired. Normal and XP cells contained approx the same amounts of alkylated guanine immediately after treatment with an alkylating agent. The loss of 7-alkylguanine from DNA was similar in both cell lines, but there was a significant difference in the elimination of O⁶-alkylguanine. O⁶-Alkylguanine in normal cells was reduced to 28% of the initial amount 48 hr after MNU treatment and to 9% 48 hr after ENU treatment. In the XP cells there were still 63% (MNU) and 70% (ENU) of the initial O⁶-alkylguanine 48 hr after treatment. These results indicate that XP cells possess a defect in the repair of DNA damage caused by alkylating carcinogens. (22 refs.)

77-0781 Prenatal and Postnatal Toxicity Induced in Guinea pigs by Nitrosomethylurea. (Eng.) Epstein, S. S.; Hasumi, K.; Iqbal, Z. M. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975*. Walker, E. A.; Bogovski, P.; Gričute, L.; David, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 435-441; 1976.

An investigation was made of the toxic effects of nitrosomethylurea (NMU) and nitrosomethylurethane (NMUT) in the offspring of treated pregnant white Hartley guinea pigs 550-700 g in wt. NMU was administered po to pregnant guinea pigs at max tolerated doses from days 34 to 58 of pregnancy, after the completion of organogenesis. NMU induced marked embryotoxic effects, as indicated by a high incidence of stillbirths and reduced birth wts, and marked postnatal effects, as evidenced by persistent stunting, high mortality during the first 8 mo of life, and extensive fatty degeneration of the liver. These toxic effects were not, however, associated with teratogenicity or prematurity. NMUT failed to induce embryotoxicity or postnatal toxicity. (10 refs.)

77-0782 Somatic Mutation as the Basis for Malignant Transformation of BHK Cells by Chemical Carcinogens. (Eng.) Bouck, N. (Dept. Microbiology, Univ. Illinois Medical Center, Chicago, IL 60612) *Nature* 264(5588): 722-727; 1976.

The somatic mutation as the basis for the malignant transformation of BHK cells by chemical carcinogens is studied. The established quasi-diploid hamster line BHK21/cl 13 and the carcinogens nitrosomethylurea (NMU) and 4-nitroquinoline-1-oxide (NQO) were used. NMU transformed efficiently. The max transformation frequency observed was 3.8×10^{-5} transformant per treated cell, 4×10^{-4} transformant per survivor, an almost 300-fold increase over the spontaneous frequency. NQO transformed effectively, even at doses where survival was unaffected. The max transformation frequency observed was 4×10^{-6} per treated cell and 2.2×10^{-5} per survivor, a 30-fold increase over the spontaneous frequency. Transformed colonies resulting from the carcinogen treatments were selected, purified by recloning, and split to high (38.5 C) and low (32 C) temperatures where they were grown and tested for the expression of the normal phenotype assessed as a significant depression in absolute and relative plating efficiency in soft agar. Some clones remained fully transformed at both temperatures. Fifty-three percent of the NMU-transformed clones and 55% of the NQO-transformed clones displayed this unconditional phenotype. The remainder of clones tested expressed the normal phenotype at one of the temperatures and the transformed phenotype at the other. The majority of these temperature restricted clones were transformed at the high temperature, normal at the low, as was expected, since transformants were initially seeded as clones growing in agar at 38.5 C. The frequency with which

the cell line Me₂N₄ reverted to normal following ethylmethane sulfonate (EMS) mutagenesis was determined by growing EMS-treated cells at 38.5°C in methylcellulose containing 5-fluorodeoxyuridine to enrich for normal revertants. The number of revertants induced by EMS in the original population was estimated to be 4×10^{-6} per treated cell, 1×10^{-2} per survivor. The chemically-induced BHK transformants were similar to many well documented somatic cell mutants. The most reasonable explanation for these transformants is that they result from a somatic mutation. (56 refs.)

- 77-0783 Pathology of Tumors Developed in Guinea Pigs Given Intraperitoneal Injections of N-Methyl-N-nitrosourea.** (Eng.) Rao, M. S. (Dept. Pathology, Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL 60611) Reddy, J. K. *Neoplasma* 24(1): 57-62; 1977.

The carcinogenic effects of repeated ip injections (10 mg/kg/wk for 18 wk) of N-methyl-N-nitrosourea (MNU) were studied in inbred male guinea pigs of NIH strain 13. Twenty of 42 animals died before 22 wk, mostly due to peritonitis or pneumonia; during the same period 2/10 control animals died of peritonitis. Of the 22 surviving MNU-treated animals, 11 developed tumors between 24 and 50 wk. The tumors included adenocarcinoma of the pancreas (2 animals), fibrosarcoma of the mesentery (2), angiosarcoma of the mesentery (2), mesothelioma of the peritoneum (1), and tumors of the small intestine (3). There seemed to be no predilection for any organ or any specific tumor. The local effects of MNU after ip injection and the absence of tumors at distant sites suggest rapid hydrolysis to an active carcinogenic intermediate and further conversion to noncarcinogenic metabolites before the compound is absorbed into the circulation. Histologically, the broad spectrum of tumors indicates susceptibility of various types of tissue to MNU and dispersion of the carcinogen locally after ip injection. (12 refs.)

- 77-0784 Sister Chromatid Exchanges Induced by Mutagenic Carcinogens in Normal and Xeroderma Pigmentosum Cells.** (Eng.) Wolff, S. (Lab Radiobiology, Univ. California, San Francisco, CA 94143) Rodin, B.; Cleaver, J. E. *Nature* 265(5592): 347-349; 1977.

Sister chromatid exchanges (SCE) induced by several carcinogens were compared in normal and xeroderma pigmentosum (XP) cells. Human fibroblasts from a normal donor and from an excision-repair-deficient XP patient (XP12) were treated with various concentrations of 4-nitroquinoline-1-oxide (4NQO), methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), N-methyl-N-nitrosoguanidine (MNNG), ethylnitrosourea (ENU) dimethyl sulfate (DMS), and mitomycin C (MMC). The control yields of SCE's in normal and XP12 cells were similar to one another and fell within the range previously reported for many cell types. Once exposed to the chemicals, however, the XP12 cells con-

tained higher numbers of SCEs than normal cells, even at concentrations too low to have detectable effects on normal cells. Since XP cells cannot perform excision-repair of damage induced by 4NQO, the elevated levels of SCEs observed after 4NQO treatment can be correlated with unrepaired damage. The same correlation cannot be made with damage induced by MMS, EMS, ENU, DMS, and MNNG, because XP and normal cells seem to undergo similar amounts of excision repair after exposure to these agents. The correlation cannot be made with damage induced by MMC either, because XP cells, which have been reported to be defective in unscheduled synthesis, respond as repair-proficient cells for the induction of chromosome aberrations. These observations, and the apparent lack of correlation between SCE frequencies and either chromosome aberration frequencies or cell killing, indicate that SCEs may be the result of fundamentally different cellular events and lesions. Since chromosome alterations are associated with cell death, SCEs may be more representative of events compatible with cell survival, including mutagenesis. The measurement of SCEs in XP cells is the most sensitive indicator to date for detecting the chromosomal effects of potential mutagens and carcinogens in mammalian cells. (31 refs.)

- 77-0785 Alkali-Labile Colicinogenic Factor EI DNA Molecules Formed in the Presence of N-Methyl-N'-nitro-N-nitrosoguanidine.** (Eng.) Mizusawa, H. (Cancer Inst., Japanese Foundation for Cancer Res., Kami-Ikebukuro Toshima-ku, Tokyo, Japan) Tanaka, S.; Kobayashi, M.; Koike, K. *Biochem Biophys Res Commun* 74(2): 570-576; 1977.

Plasmid colicinogenic factor EI DNA molecules (ColEI DNA) of *Escherichia coli* were used as target molecules to analyze the structural modification of DNA by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). At $1 \mu\text{g}/\text{mL}$ MNNG, both cell growth and overall DNA synthesis were neither stimulated nor inhibited, and plasmid DNA molecules were isolated as closed circles after replication. These molecules were stable following ribonuclease treatment, but they were susceptible to alkaline hydrolysis. Such alkali-labile sites of ColEI DNA were found in the parental strands, and they were randomly distributed from the restriction endonuclease EcoRI cleavage site. Because the alkali-labile site was formed at the EcoRI cleavage site. Because the alkali-labile site was formed on the prelabeled parental strand of ColEI closed circular DNA, it is suggested that this modification reaction is pre-mutational and not dependent on DNA replication. (14 refs.)

- 77-0786 The Effect of Ascorbate on Amine-Nitrite Carcinogenicity.** (Eng.) Fong, Y. Y.; Chan, W. C. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Poly-*

technical Institute, Tallinn, Estonian SSR, 1-3 October 1975. Walker, E. A.; Bogovski, P.; Gričiute, L.; Davis, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 461-464; 1976.

In order to determine whether an excess of vitamin C in the diet can protect rats fed with nitrosamine precursors from tumors, three groups of Sprague-Dawley rats were fed with basic diet and unadulterated tapwater (Group A), with basic diet and tapwater containing 0.5 g/liter aminopyrine and 0.5 g/liter sodium nitrite (Group B), or with a basic diet reinforced with 800 mg/kg of ascorbic acid and water containing the same compounds as for Group B (Group C). After 40 wk, the rats were killed. No rats of Group A had tumors, 15/30 in Group B had a total of 23 tumors, and 9/32 in Group C had a total of 11 tumors. The neoplasms arising in Groups B and C were composed of tumors of the lung (20 in B; 9 in C), liver (2 in B), and kidney (1 in B; 2 in C). It is concluded that the administration of ascorbic acid reduced the incidence and changed the nature of the tumors, probably due to a partial blockage of the N-nitrosation of aminopyrine. (11 refs.)

77-0787 Nitrosation of Food Amines Under Stomach Conditions. (Eng.) Walters, C. L.; Dyke, C. S.; Saxby, M. J.; Walker, R. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975.* Walker, E. A.; Bogovski, P.; Gričiute, L.; Davis, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 181-193; 1976.

The levels of salivary nitrite and thiocyanate and of gastric nitrite, thiocyanate, and phenol were estimated in healthy volunteers. The mean level of nitrite in the saliva of fed volunteers was 0.063 mM; this rose to 0.097 mM immediately after a meal containing 56-91 mg of potassium nitrate. The average nitrite level in the gastric juice of fasting volunteers was 0.014 mM; this rose to almost 0.3 mM following a meal with an overall nitrite concentration of 0.83 mM. Thiocyanate levels were higher in smokers (S) than in nonsmokers (NS) in both saliva (1.82 mM, NS; 5.45 mM, S) and in fasting gastric juice (0.45 mM, NS; 1.49 mM, S). The interaction of nitrite and food amines was investigated in vitro under conditions approximating those of the human stomach. Incubation for 3 hr of a luncheon meat slurry containing nitrite to an overall concentration of 30 mg/kg with eggs, milk, and human gastric juice at pH 2 in the presence of 1.2 mM thiocyanate resulted in the formation of 0.045 micromole (μmol)/kg of nitrosopiperidine (NPP), 0.003 μmol /kg of nitrosopyrrolidine (NPy), and 0.70 μmol /kg of dichloromethane-extractable nonvolatile nitrosamines (NVN). After four volunteers ate meals containing luncheon meat, egg, and milk with overall levels of nitrite of 0.46-0.56 mM (32-39 mg/kg), their stomach contents were analyzed for nitroso compounds:

no NPy was found, levels of NPP were 0-0.006 μmol /kg, and levels of NVN were 0-0.4 μmol /kg. (17 refs.)

77-0788 A Quantitative Estimation of the Danger of Chemical Carcinogenic Effects. (Rus.) Kuryandsky, B. A. (Lab. Toxicology, Sanitary-Epidemiological Centre, Moscow, USSR) *Vopr Onkol* 22(7): 67-72; 1976.

A formula for the quantitative estimation of the degree of blastomogenic activity of chemical substances is presented. In this formula, the blastomogenic activity of the substance (C) is directly proportional to the total number of tumor-involved organs in experimental animals (T) and the relative frequency of carcinogenesis. The activity is inversely proportional to the log of an effective carcinogen dosage mg/kg/1g ED50, a latent period of tumor development (L) in days, and the total number of involved organs in control animals (T1). Numerical values are provided for four classes of blastomogenic compounds according to this criteria: Class I (extremely high) > 0.5 , Class II (high) 0.499 to 0.1, Class III (moderately high) 0.099 to 0.05, and Class IV (low) < 0.05 . (42 refs.)

77-0789 Possible Important Role of Urinary N-Methyl-N-(3-Carboxypropyl) nitrosamine in the Induction of Bladder Tumors in Rats by N-Methyl-n-dodecyl nitrosamine. (Eng.) Okada, M. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171 Japan) Suzuki, E.; Mochizuki, M. *Gann* 67(5): 771-772; 1976.

The urinary metabolites of N-methyl-N-dodecyl nitrosamine (MDN) in rats were studied. Nine male Wistar rats were given a total of 1,287 mg by gastric intubation; the urine was collected 24 hr later. The MDN metabolites found in the urine were N-methyl-N-(carboxymethyl) nitrosamine (N-nitrososarcosine); N-methyl-N-(3-carboxypropyl) nitrosamine (MCPN) was a minor metabolite. It is concluded from these results and those published in the literature that the induction of bladder tumors in rats by po MDN is due to its urinary metabolite MCPN. (7 refs.)

77-0790 Studies on Pituitary Cells of Rats Treated with Chemical Hepatocarcinogens In Vivo. (Eng.) Ingleton, P. M. (Dept. Zoology, Univ. Sheffield, S10 2TN, England) Hancock, M. P.; Stribley, M. F. *J Endocrinol* 71(2): 77P; 1976.

Pituitary cells of rats treated with chemical hepatocarcinogens in vivo are studied. Pituitaries of rats bearing hepatomas that had been induced by feeding diethylnitrosamine (5 mg/100 ml drinking water) for 14-16 wk were examined for growth hormone content by densitometry after polyacryla-

amide gel electrophoresis and histologically by Herlant's tetrachrome staining technique. The pituitaries of rats with hepatomas contained lower concentrations of growth hormone than did those of age-related controls. Histologically, some somatotrophs in hepatoma-bearing rats had pycnotic nuclei and appeared to be dying. Electron microscope studies on pituitaries of male rats with large hepatomas demonstrated that the somatotrophs were relatively inactive, with small mitochondria, sparse rough endoplasmic reticulum and smooth plasma membranes, but were moderately well granulated. However, somatotrophs of rats bearing hepatomas induced by feeding 2-acetylaminofluorene (0.04%) seemed to be quite different. Pituitaries of six male rats that had ingested the carcinogen for 25 wk all demonstrated the presence of somatotrophs that were extremely electron-dense. The cells were very active, having well developed Golgi regions, large and numerous mitochondria, organized rough endoplasmic reticulum and numerous hormone granules, many of which were arranged peripherally. The electron density seemed to be due in part to an increase in the numbers of free ribosomes and polysomes. The hepatomas of these rats consisted of nodules up to 1.0 cm in diameter scattered throughout the liver, while the diethylnitrosamine-induced tumors were large masses of malignant tissue with little normal tissue remaining. This may represent a more terminal condition and account for the differences between the somatotrophs in the two groups. After only 5 wk of ingestion of the aminofluorene, some somatotrophs of treated rats demonstrated an increase in free ribosomes and were more active than normal cells. Because some somatotrophs of the rats treated for 25 wk showed lysosomal activity, this may indicate that the somatotrophs were becoming less active after an active phase. (3 refs.)

- 77-0791 **Autocatalysis in the Nitrosation of Dihexylamine.** (Eng.) Okun, J. D. (Dept. Nutrition Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139) *J Org Chem* 42(2): 391-392; 1977.

A novel autocatalysis reaction in the nitrosation of dihexylamine is reported. The initial rates of dihexylamine nitrosation at four different nitrite concentrations (30, 40, 50, and 60 mM) were as expected for the nitrosation of a secondary dialkylamine and yielded a second-order rate constant of $0.0004 \text{ M}^{-2}/\text{sec}$ at pH 3.5. At each nitrite concentration, however, the reaction rate increased abruptly by a hundredfold beginning at a dihexylnitrosamine concentration of $2 \times 10^{-5} \text{ M}$. The reaction rates were proportional to the square of the nitrite concentration in both the initial and catalytic regions of the reaction. Reaction mixtures, which were initially clear, colorless solutions, became cloudy at the point when the rate began to increase. In experiments with dipentylamine and dibutylamine, no autocatalytic effect was observed nor was a cloud point seen. When dihexylamine was added with an equimolar concentration of either dipentylamine or dibutylamine and the resulting solution nitrosated, however, both

amines showed increased rates of nitrosation. It is suggested that as the concentration of dihexylnitrosamine exceeds its solubility in aqueous solution, spontaneous emulsification occurs. Hydrophobic interactions lead the amine to concentrate in the dihexylnitrosamine microdroplets and catalysis occurs in a manner analogous to that observed in the presence of added surfactant. (6 refs.)

- 77-0792 **Formation In Vivo of Volatile N-Nitrosamines in Man After Ingestion of Cooked Bacon and Spinach.** (Eng.) Fine, D. H. (Thermo Electron Cancer Res. Center, 85 First Ave., Waltham, MA 02154) Ross, R.; Rounbehler, D. P.; Silvergleid, A.; Song, L. *Nature* 265(5596): 753-755; 1977.

The in vivo formation of volatile N-nitrosamines in man after ingestion of a midday meal consisting of a bacon, spinach, and tomato sandwich and beer was investigated. Blood (20 ml) was taken on the day before the test and on the day of the test, 50 min before the meal. Lunch consisted of 310 g of spinach, 170 g of cooked bacon, 200 g of tomatoes, 120 g of bread, and 460 g of beer. One percent of the total lunch was analyzed for volatile N-nitrosamines. Blood samples were also taken 35, 65, 162, and 220 min after the meal. A final control sample was taken at 1,300 min. Control experiments were performed by recovering N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), and N-nitrosopyrrolidine (NPYRR) at the $0.4\text{-}\mu\text{g}/\text{kg}$ level from whole human blood. The meal contained preformed NDMA and NPYRR. The total amount of preformed NDMA ingested was 1,600 nanograms (ng). The amount of NDMA and NDEA present as a function of time in the blood (assuming total body blood was 5,640 ml) was determined. Before the meal, the blood contained 2,000 ng of NDMA and 510 ng of NDEA. Thirty-five minutes after the meal, NDMA had increased to 4,350 ng and NDEA to 570 ng; 65 min after the meal, NDMA had fallen to 860 ng but NDEA had increased to 2,600 ng. At 162 min, both had decreased below pre-meal levels. At 1,300 min, there were 760 ng of NDMA in the blood, and NDEA was not present. NPYRR was not detected in the blood either before or after the meal. The experiments demonstrate conclusively that N-nitrosamines can be formed in vivo in man after the ingestion of conventional foodstuffs. (11 refs.)

- 77-0793 **Factors Affecting the Induction of Dimethylnitrosamine Demethylase by Aroclor 1254.** (Eng.) Guttenplan, J. B. (Dept. Biochemistry, New York Univ. Coll. Dentistry, New York, NY 10010) Garro, A. J. *Cancer Res* 37(1): 329-330; 1977.

The enzyme-inducing effect of Aroclor in dimethylnitrosamine (DMN) metabolism was clarified in Swiss Webster mice. The microsomal dimethylnitrosamine demethylase activity (in nanomoles of formaldehyde/mg protein/min) after

Aroclor and corn oil pretreatment (controls), respectively, was 7.7 and 3.5 (15-min incubation, normal protein test diet); 12.1 and 5.8 (15-min incubation, standard chow); and 8.1 and 3.7 (40-min incubation, normal protein diet). Aroclor pretreatment consisted of single ip injections of 500 mg/kg 4 days before sacrifice. Aroclor-induced microsomes lost 80% DMN demethylase activity during a 60-day frozen storage in liquid nitrogen, compared to a 50% loss for untreated microsomes. Despite the storage loss, no reduction in the mutagenic activation of DMN was found. (12 refs.)

77-0794 Studies on the Effect of Feeding Nitrite and Secondary Amines to Wistar Rats. (Eng.) Telling, G. M.; Hoar, D.; Caswell, D.; Collings, A. J. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975.* Walker, E. A.; Bogovski, P.; Gričute, L.; Davis, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 247-254; 1976.

Estimation was made of the production of nitrosopyrrolidine (NPy) and nitrosodimethylamine (NDMA) in the stomachs of Wistar rats fed diets containing pyrrolidine (Py) or dimethylamine (DMA). When 1 g/liter of sodium nitrite was added to the drinking water, nitrosamines were found at levels greater than background only when the levels of dietary DMA or Py exceeded 1 g/kg. With 2 g/kg Py, the mean increase in NPy over controls was 124 nanograms (ng)/stomach; with 2 g/kg DMA, the mean increase in NDMA was 13 ng/stomach. Due to the existence of such a "threshold," in considering nitrosamine formation in vivo it is unrealistic to extrapolate from high dietary concentrations of secondary amines to those found in practice, which rarely exceed 1 g/kg in normal human diets. The concentration of dietary amine had a greater influence on nitrosamine formation than did the concentration of nitrite in the drinking water. This finding is in contradiction to the current kinetic theory of nitrosamine formation, in which formation is predicted to be proportional to the square of the nitrite concentration. (11 refs.)

77-0795 Toxic and Carcinogenic Effects of Nitrosodimethylamine in Mink. (Eng.) Koppang, N.; Rimeslatten, H. In: *Environmental N-Nitroso Compounds: Analysis and Formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975.* Walker, E. A.; Bogovski, P.; Gričute, L.; Davis, W., eds. International Agency for Research on Cancer. (Lyon, France): IARC Scientific Publications No. 14, pp. 443-452; 1976.

Toxicological observations were made in groups of mink that received 0.04-0.17 mg/kg/day of dietary nitrosodimethyla-

mine (NDMA). After 122 days, no pathological changes were seen in 59 animals fed cumulative doses of < 10 mg/kg NDMA, but some of the smaller hepatic veins were partially occluded in the livers of animals fed cumulative doses of 16-21 mg/kg NDMA. Prolonged feeding of 20 animals with 0.13-0.17 mg/kg/day NDMA resulted in the death of one male mink from liver fibrosis and occlusive changes in the hepatic veins, after a total uptake of 26 mg/kg. Sixteen other animals developed hemangiomatous liver tumors after a total intake of 25-87 mg/kg NDMA. It is concluded that NDMA is very carcinogenic in mink, provided that the dose applied approaches hepatotoxic levels and long exposures are used. (5 refs.)

77-0796 Importance of DNA Repair in the Organ Specificity of Tumour Induction by N-Nitroso Carcinogens. (Eng.) Pegg, A. E.; Nicoll, J. W.; Magee, P. N.; Swann, P. F. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975.* Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. (New York: American Elsevier Publishing Co., Inc.): Vol. 17, pp. 39-54; 1976.

A study was made of the relationship between tumor incidence in particular organs of the rat after treatment with dimethylnitrosamine (DMN) or diethylnitrosamine and the formation and persistence of various alkylated nucleosides in DNA. There was a good correlation between the formation and persistence in DNA of 06-alkylguanine and tumor incidence; ie, after a large dose of DMN (20 mg/kg), which produces tumors of the kidney but not of the liver, 06-methylguanine was shorter-lived in liver DNA ($t_{1/2} = 19$ hr) than in kidney DNA. In kidney DNA, after an initial fall of some 30% over the first 20 hr, the loss occurred at an extremely slow rate. The loss of 7-alkylguanine took place at a similar rate in both tissues: after 20 mg/kg DMN, loss from liver DNA occurred with $t_{1/2} = 58$ hr and from kidney DNA with $t_{1/2} = 52$ hr. It is suggested that the formation and persistence until cell division of promutagenic products such as 06-alkylguanine might be responsible for tumor initiation and that the differing abilities of cells in various organs to catalyze the repair of these products might account for part of the differing susceptibilities of tissues to nitrosamines. (61 refs.)

77-0797 The Carcinogen Ethionine Elevates Progesterone Levels. (Eng.) Sharma, O. K. (Dept. Microbiology, Univ. Colorado Medical Center, 4200 East Ninth Ave., Denver, CO 80262) *Nature* 265(5596): 748-749; 1977.

The effect of ethionine (E) and several of its analogs and metabolites on progesterone levels was evaluated. There was a rigid structural requirement for E in the induction of ovalbumin synthesis in the immature chick oviduct. Ovalbumin

synthesis produced by ethionine sulfoxide was less extensive than that produced by E. In the rat, E was metabolized to E sulfoxide, N-acetyethionine, and N-acetyethionine sulfoxide, but E sulfoxide and N-acetylE could be converted back to E. In the chick, the metabolism of N-acetylE was different, as it failed to induce ovalbumin synthesis. The sulfone derivative of E and its propyl homolog failed to elicit the synthesis of ovalbumin. The administration of E plus adenine elevated serum progesterone levels up to tenfold but it had no significant effect on the levels of 17- β -estradiol. Progesterone was incapable of inducing cytodifferentiation of tubular gland cells or ovalbumin synthesis in the unstimulated immature chick oviduct. E and progesterone produced no pronounced effects on specific protein synthesis without previous estrogen stimulation. Serum samples were resubmitted for analysis after storage for 1 mo at 15 C. In no case was the variation greater than twofold. Increase in cholesterol synthesis in the rat was induced by the administration of E, aflatoxin, N-2-fluorenylacetylamide, and 3-methyl-4-dimethylaminoazobenzene. The effect was thought to be a loss of feedback control of synthesis by dietary cholesterol. The elevation in cholesterol levels may increase the progesterone levels. The increase of serum progesterone levels caused by E may be the result of increased synthesis of progesterone or decreased degradation or excretion. (23 refs.)

- 77-0798 β -Retinoic Acid Inhibits and Reverses Testosterone-Induced Hyperplasia in Mouse Prostate Organ Cultures.** (Eng.) Chopra, D. P. (Southern Res. Inst., 2000 Ninth Ave., South, Birmingham, AL 35205) *Nature* 265(5592): 339-341; 1977.

The effects of β -retinoic acid (RA) and other retinoids on testosterone-induced lesions were investigated in the mouse prostate system. Ventral prostates from 8- to 10-wk-old C3H mice were removed and studied in two series of experiments. In the first, explants were incubated simultaneously with testosterone (1.8×10^{-5} M) and different concentrations of RA. In the second, the explants were allowed to develop hyperplasia by treatment with the testosterone for 8 days, after which they were treated with testosterone and different concentrations of RA for an additional 48 or 96 hr. The changes in cell proliferation caused by testosterone or RA were determined by the colcemid metaphase arrest technique. Testosterone stimulated cellular proliferation in the prostate epithelium at 4 or 8 days after treatment; however, this effect was prevented in explants simultaneously treated with RA. Treatment of explants with testosterone produced hypertrophy and hyperplasia of the alveolar epithelium. In the explants treated simultaneously with testosterone and RA (1.7×10^{-5} M), the degree of hypertrophy and hyperplasia was significantly less than that of explants that received the hormone only. In the explants treated with testosterone for 8 days followed by simultaneous treatment with testosterone and RA at 1.7×10^{-5} , 3.3×10^{-6} , and 6.6×10^{-7} M, the hyperplasia was reversed. The inhibition of testosterone-induced

hyperplasia by RA may be accomplished by inhibiting the binding of testosterone to the specific protein and/or the metabolism of testosterone. (21 refs.)

- 77-0799 Radioimmunoassays for Monitoring Exposure to Potential Carcinogens.** (Eng.) Gutierrez-Cernosek, R. M. (Biochemistry Dept., Univ. Arkansas Medical Sciences, Little Rock, AR 72201) *Ann Clin Lab Sci* 7(1): 35-41; 1977.

Radioimmunoassays for measuring two known animal carcinogens, 2-actylaminofluorene (2-AAF) and diethylstilbestrol (DES), and their metabolites have been developed and validated. To obtain urines for the measurement of 2-AAF metabolites, C3H female mice were fed chow containing 500 ppm 2-AAF for 5 days. Human urines were spiked with solutions of 7-OH-2-AAF. To obtain urines for measuring the principal urinary metabolite of DES, DES monoglucosiduronate (DES Mono), female mice were fed chow containing 100 ppb DES for 2-3 days. Human urines were spiked with solutions of DES Mono. The rabbit antiserum developed for the 2-AAF procedure recognized 7-OH-AAF and AAF almost equally well. The usable concentration range for 7-OH-AAF is 836 picomoles to 84 femtomoles. The antiserum developed for the DES procedure also showed almost equal recognition of DES and DES Mono. The usable concentration range of DES Mono with this antiserum was 2.4 picomoles to 11 femtomoles. For DES, the usable concentration range was 1.9 picomoles to 26 femtomoles. The validity of the test results was demonstrated using the spiked human urine samples. It is concluded that radioimmunoassay is the simplest and most sensitive technique for monitoring human exposure to carcinogens and potential carcinogens. (19 refs.)

- 77-0800 Prenatal Exposure to Diethylstilbestrol in Mice: Toxicological Studies.** (Eng.) McLachlan, J. A. (Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC 27709) *J Toxicol Environ Health* 2(3): 527-537; 1977.

The influence of prenatal exposure to diethylstilbestrol (DES) on the postnatal development of male and female genital tract function was evaluated in CD-1 mice. The plasma disappearance of 14 C-DES, following its iv administration to mice pregnant for 16 days, was determined. The disappearance curve was resolved into four major components, with half-lives of 4 sec, 1 min, 13 min, and 14 hr. 14 C-DES levels in the placenta were higher than the levels in the fetus until almost 0.5 hr after injection. The initial movement of DES from the mother to the fetus was restricted, probably by the placenta. However, the drug eventually reached the fetal compartment and accumulated in the fetal reproductive tract. Genital tract lesions contributed to the infertility in DES-treated female

mice (6-15 mo old). The incidence of these lesions, which included cystic hyperplasia of the endometrium and uterine adenocarcinoma, was dose-related. Histological changes, such as glandular elements and cellular atypia, were observed in the vaginal epithelium. Epidermoid tumors of the cervix and vagina were also noted. Squamous metaplasia was found in the oviducts, uterus, and cervix in females derived from DES-treated mice but not in the corresponding controls. Alterations were seen in the genital tracts of 75% of the male offspring of mice treated with 100 µg/kg DES. Nodular enlargements of the seminal vesicle and/or prostate were found in 8/24 mice. In five of these animals, the enlargements were associated with squamous metaplasia. Adjacent to and in the duct of the coagulating gland of the prostate of one DES-exposed offspring, there were downgrowths and cellular pleomorphism, suggesting a more serious, possibly preneoplastic, growth disturbance. In newborn males obtained from corn oil-treated mothers, Wolffian- but not Mullerian-derived tissues were easily identified. However, in the corresponding neonates from mice treated with DES (100 µg/kg) during pregnancy, both Mullerian and Wolffian duct tissue were present. Mullerian duct tissue may represent a site for the transplacental toxicity of DES in both the female and male fetus. (28 refs.)

77-0801 Male Genitourinary Abnormalities and Maternal Diethylstilbestrol. (Eng.) Cosgrove, M. D. Dept. Urology, Los Angeles County- Univ. Southern California Medical Center, Los Angeles, CA) Benton, B.; Henderson, B. E. *J Urol* 117(2): 220-222; 1977.

Maternal diethylstilbestrol (DES) ingestion and male genitourinary abnormalities were investigated. A health questionnaire was mailed to the mothers of 306 boys exposed to DES and to 231 controls. The questions concerned general health, congenital abnormalities, genitourinary problems, and cancer. Completed questionnaires were returned by 225 (73%) of the mothers treated with DES, compared to 111 (48%) of the controls. The 34 mothers whose responses were most suggestive of congenital genitourinary abnormalities in their male offspring were invited to bring their sons for clinical examination. A full medical history, complete physical examination, and urinalysis were performed by a urologist on the 15 boys who responded to this invitation. Gestational age was lower at first visit in fetuses exposed to DES, although the mothers' wts were similar at that time. The lower birth wt of boys exposed to DES could be correlated with the shorter length of gestation than the controls. When the percentage of mothers prescribed various other medications during pregnancy was compared, the mothers treated with DES received more progestin and other estrogens than did the control group. Although the incidence of a history of cancer, heart disease, asthma, and appendicitis was similar in the two groups, significantly more mothers treated with DES reported genitourinary symptomatology and penile abnormalities in their male children than did the controls. Ten mothers of boys exposed to DES volunteered descriptions of urethral

obstruction generally requiring an operation, compared to no such reports in the control group. The likelihood of congenital genitourinary pathology seemed highest in 34 cases, 26 boys exposed to DES and 8 controls. Attempts to locate these subjects for an examination resulted in 15 examinees, 11 exposed to DES and 4 controls. Three of 4 controls but only 2/11 DES-exposed subjects were found to have no obvious urological abnormalities. The three cases of undescended testis in the latter were all unilateral, and they had been corrected surgically. They were not associated with hypospadias, although two cases had coexistent meatal stenosis. More extensive clinical studies should be undertaken to determine the level of risk to which many young men are subject. (14 refs.)

77-0802 Effect of Corn Oil and Estradiol Dipropionate Administered per os upon the Hypophysis and Reproductivity of Mice of the T. M. Strain. (Eng.) Boschetti, N. V. (Dept. Anatomy, Univ. Puerto Rico Sch. Medicine, San Juan, Puerto Rico) *Ann Histochem* 21(4): 335-343; 1976.

The effects of feeding corn oil and estradiol dipropionate on the reproductive ability and pituitary integrity of TM mice were investigated. TM mice fed 150-200 mg/day corn oil containing 1 µg of estradiol dipropionate reproduced very poorly compared to control mice. Some females were completely sterile, and others of the first seven generations maintained under the same regimen reproduced only once, becoming sterile thereafter. None of the mice of the eighth generation reproduced. There were no mature follicles or corpora lutea in the ovaries of the female mice of the last generation, and there were no mature spermatozoa in the testes of the males. The pituitary glands of the mice were depleted of gonadotrophic hormones, and a considerable decrease in pituitary acidophilic and basophilic cells was observed. The incidence of pituitary tumors (chromophobe adenomas of the pars distalis and intermediate lobe tumors) was > 15%, compared to 0% in control animals fed no corn oil and 1.2% in control animals fed corn oil plus free fatty acids. (7 refs.)

77-0803 Influence of High Dose of Estradiol on ICRC Mouse Bearing Transplanted Mammary Tumors. (Eng.) Pai, S. R. (Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay) Save, P. G. *Indian J Med Res* 64(12): 1788-1792; 1976.

The effects of estradiol on gonadectomized ICRC mice inoculated with transplanted mammary tumors or mammary tumor virus (MTV) obtained from acellular extracts of these mammary tumors were studied. The leukemoid reaction (splenomegaly and granulopoiesis) occurred in intact female syngeneic mice (24/50) and in syngeneic males (2/20) inoculated sc with a 10% mammary tumor homogenate containing intact tumor cells. The leukemoid reaction also was observed in 6/9 gonadectomized ICRC mice receiving mammary tumor cell homogenate and in 9/10 which got the mammary

tumor cell homogenate accompanied by 10 μ g estradiol. Lymphocytic leukemia developed in all groups treated with estradiol. Administration of 10 μ g estradiol for 18 days induced lymphocytic leukemia in 1/10 gonadectomized ICRC treated with MTV-containing mammary tumor homogenates; 1/12 treated with MTV-containing acellular extracts; and 2/12 treated with estradiol alone. Immunological responses of gonadectomized mice receiving 9 or 18 injections of 10 μ g estradiol daily showed that cellular and humoral immunity of the mice was unaffected. (26 refs.)

- 77-0804 Relationship of Oral Contraception to Development of Trophoblastic Tumour After Evacuation of a Hydatidiform Mole.** (Eng.) Stone, M. (St. George's Hosp., Hyde Park Corner, London, SW1, England) Dent, J.; Kardana, A.; Bagshaw, K. D. *Br J Obstet Gyn* 83(12): 913-916; 1976.

The relationship of oral contraceptive use to the increased need for cytotoxic drug treatment of trophoblastic tumor after evacuation of a hydatidiform mole was investigated. Of the 611 patients studied, none was followed for less than 1 yr and some for as long as 42 mo. Most had completed 2 yr of follow-up. Urine samples were estimated for human chorionic gonadotrophin (HCG) every 2 wk until normal values were recorded, then monthly for 1 yr after hydatidiform mole evacuation, and quarterly during the second year of follow-up. The need for cytotoxic drugs for trophoblastic tumor was at least two times as great when oral contraceptives were taken before normal HCG values had been obtained. The taking of oral contraceptives after HCG values had become normal apparently did not increase the need for drug treatment. Exogenous sex steroid hormones probably cause a true increase in the number of patients developing choriocarcinoma or invasive moles. It is possible that sex steroids might exert their tumor stimulating effect via the immune system. However, patients undergoing treatment for trophoblastic tumors have been assessed with respect to both cell-mediated humoral responses, and significant immunosuppression has not been observed. The plasma clearance of folic acid is increased in women taking oral contraceptives. An earlier study showed that folate deficiency was common in patients with trophoblastic tumors, but a causal relationship has not been established. Ten percent of the patients in this study had lesions that failed to regress spontaneously, which may be partly explained by the greater use of oral contraceptives after evacuation. This may account for the high proportion of patients (more than 20%) receiving cytotoxic drugs in some North American series. (14 refs.)

- 77-0805 Endometrial Carcinoma and Oral Contraceptive Agents.** (Eng.) Cohen, C. J. (Dept. Obstetrics Gynecology, Mount Sinai Hosp., 1176 Fifth Ave., New York, NY 10029) Deppe, G. *Obstet Gynecol* 49(4): 390-392; 1977.

Six patients who took oral contraceptives for 5-18 yr developed endometrial cancer. Four had adenocarcinoma and two, severe adenomatous hyperplasia. Five took a sequential agent (Oracon) while one received Ovral. An additional patient who took Premarin and Provera sequentially developed adenocarcinoma of the endometrium. Progesterone may not completely protect the user against the endometrial cancer causing potential of the estrogens. (12 refs.)

- 77-0806 Estrogens and Endometrial Carcinoma.** (Eng.) Gray, L. A. (Dept. Obstetrics, Gynecology, Univ. Louisville Sch. Medicine, Louisville, KY 40202) Christopherson, W. M.; Hoover, R. N. *Obstet Gynecol* 49(4): 385-389; 1977.

The previous use of exogenous estrogens by 205 endometrial cancer patients was compared with that of 205 matched controls who were free of endometrial cancer at the time of hysterectomy. The measure of strength of the association used is the relative risk (RR) as approximated by relative odds. In the cancer group 32 patients had used conjugated estrogens, compared to 12 in the control group, giving an RR of 3.1 ($P=0.0008$). The RR for nonconjugated estrogens was 2.9, and for estrogens given im, 2.3. There was no evidence of risk among those using the hormone (dosage, < 1.25 mg tablets) for less than 5 yr; the RR was 11.5 for those using it for 10 yr or more. The RR for users of the 1.25 mg tablets was 12.7, compared to an RR of 2-4 for users of 0.625 mg or 0.3 mg tablets. (32 refs.)

- 77-0807 Metabolic Activation of 2,4-Diaminoanisole, a Hair-Dye Component--I. Role of Cytochrome P-450 Metabolism in Mutagenicity In Vitro.** (Eng.) Dybing, E. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway) Thorgeirsson, S. S. *Biochem Pharmacol* 26(8): 729-734; 1977.

The activation of 2,4-diaminoanisole (DAA) to a mutagen in the *Salmonella* test system was studied using liver fractions from rats or mice treated with inducers of the cytochrome P-450 system β -naphthoflavone (BNF: 80 mg/kg in corn oil, ip, 48 hr before liver removal) gave 2,077 revertants/plate when rats were used compared to 252 with controls. BNF given to mice resulted in 920 revertants; the control value was 473. The next most effective activator was phenobarbital, which gave 485 revertants when given to rats, and 630 when given to mice. The enzyme for activating DAA to a mutagen were found in both the microsomal and postmicrosomal fraction (PMF). When liver fractions from rats treated with BNF were used (at 2 mg protein/test plate), 237 revertants were produced with the microsomal fraction, 23 with the PMF and 873 when these two fractions were combined. Similar results were obtained with mice. It is suggested that formal

on of hydroxylamines from DAA may be necessary in the activation of DAA to a mutagen. (29 refs.)

77-0808 Electrochemical Properties of Polycyclic Compounds Studied by the Polarographic Method in Anhydrous Systems. III. Polarographic Reduction Potentials of Carcinogenic Nitrogen Compounds in Dimethylsulfoxide. (Eng.) Podany, V. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia) Vachalkova, A.; Vachalka, L. *Neoplasma* 23(6): 617-622; 1976.

The polarographic reduction potentials of carcinogenic nitrogen compounds in anhydrous dimethyl sulfoxide (DMSO) solution containing 0.15 M tetrabutylammonium perchlorate as the supporting electrolyte were evaluated. The compounds yielded well-developed current-voltage curves that were suitable for determining reduction half-wave potentials. All polarograms of the aza-compounds showed two or three well-defined waves except for carbazole and 1,2,7,8-benzcarbazole, which were reduced in only one polarographic wave and at a significantly negative potential. The values of the half-wave potentials determined in DMSO were nearly identical with those determined in dimethylformamide (DMF). A shift of the half-wave potentials toward positive values in DMSO was very small in comparison with the values measured in DMF--the differences in the values between DMSO and DMF were from 0.000 to 0.080 volt. An exception occurred with carbazole, for which the difference between potentials was 0.180 volt. 6,12-Diazaanthanthrene yielded identical first polarographic waves in both solvents. The noncarcinogen 1,2,7,8-dibenzo-6,12-diazaanthanthrene yielded no polarographic waves in DMSO. The diffusion current for the first reducing polarographic waves was directly proportional to concentration in the range 1×10^{-3} to 1.8×10^{-4} M. Concentration had no effect on the half-wave potentials in the range 1×10^{-3} to 1×10^{-4} M. To verify the reduction mechanism of the aza-compounds in DMSO, the polarographic current-voltage curves were subjected to a logarithmic analysis. The calculated values for the first polarographic wave agreed with the theoretical value of 0.059 volt, which corresponded to a one-electron reduction. However, the values calculated by logarithmic analysis for the second cathodic polarographic wave were higher than 0.059 volt. The polarographic behavior of polycyclic nitrogen compounds in DMSO is very similar. (18 refs.)

77-0809 Action of 7-Bromomethylbenz(a)anthracene on Isolated Transfer Ribonucleic Acids. (Eng.) Massouh-Rizk, L.; Keith, G.; Dirheimer, G. In: *The Prediction of Chronic Toxicity from Short Term Studies. Proceedings of the European Society of Toxicology held at Montpellier, June 1975*. Duncan, W. A.; Leonard, B. J.; Brunaud, M., eds. New York: American Elsevier Publishing Co., Inc.: Vol. 17, p. 419-431; 1976.

The carcinogen 7-bromomethylbenz(a)anthracene was reacted with the following transfer RNA's (tRNA's) from brewer's yeast: tRNA-Phe, tRNA-Asp, tRNA-Trp, and tRNA-Arg/III. Analysis of oligonucleotides obtained after T_1 or pancreatic digestions of the modified tRNA-Phe demonstrated that the methylbenzanthracene nucleus was primarily fixed on the octanucleotide -G-G₁₉-G₂₀-A₂₁-G-A-G-Cp located in the hU loop of tRNA-Phe. Further-modified tRNA-Phe species were also obtained that contained two to three modification sites, probably at G₁₉, G₂₀, and A₂₁. Modification at the G₇₁ residue of tRNA-Asp was observed. The biological activity of all the modified tRNA's to participate in amino acid-accepting reactions was diminished. (36 refs.)

77-0810 Alkylation of a Tripeptide by a Carcinogen: The Crystal Structures of Sarcosylglycylglycine, 9-Methyl-10-chloromethylanthracene, and Their Reaction Product. (Eng.) Glusker, J. P. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111) Carrell, H. L.; Beriman, H. M.; Gallen, B.; Peck, R. M. *J Am Chem Soc* 99(2): 595-601; 1977.

To investigate the molecular basis of chemical carcinogenesis by polycyclic aromatic hydrocarbons, the molecular structures of covalent compounds formed between hydrocarbons and portions of biological macromolecules was studied by x-ray crystallography. The tripeptide sarcosylglycylglycine (SGG) reacted with 9-methyl-10-chloromethylanthracene, with the elimination of hydrochloric acid, to form the alkylated tripeptide. The location of the hydrogen atoms showed that both SGG and the alkylated tripeptide existed as zwitterions, the C-terminal carboxyl groups being ionized and the N-terminal nitrogen atoms bearing positive charges. Because the anthracene was disordered in the approx ratio 3:1, the molecular dimensions were less than accurate. There were no significant changes in dimensions upon alkylation of the tripeptide compared with both the simple peptide and the alkylating agent except at the point of alkylation. The conformations of the two tripeptides differed, and one peptide group in the alkylated tripeptide was nonplanar. This nonplanar peptide conformation occurred in the peptide group farthest from the alkylation site. The major difference in conformation for SGG upon alkylation occurred at the C(7)-C(8) bond. Since each peptide occurred as a racemate in the crystals studied, the signs of all torsion angles were changed for the mirror image of each molecule. There was no water of crystallization present in SGG, and the packing was described as a network of hydrogen bonds in all directions. However, the alkylated tripeptide had two molecules of water of crystallization per peptide molecule, and the packing was much simpler. The study shows the influence of alkylation by a bulky hydrophobic group on the conformation of a peptide in the crystalline state. (34 refs.)

77-0811 High Microsome-mediated Mutagenicity of the 3,4-Dihydrodiol of 7-Methylbenz[a]anthracene

in *S. typhimurium* TA 98. (Eng.) Malaveille, C. (Unit Chemical Carcinogenesis, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69008 Lyon, France) Tierney, B.; Grover, P. L.; Sims, P.; Bartsch, H. *Biochem Biophys Res Commun* 75(2): 427-433; 1977.

7-Methylbenz(a)anthracene and its 1,2-, 3,4-, 5,6- and 8,9-dihydrodiols were tested for mutagenicity towards *Salmonella typhimurium* TA 98 in the presence of a rat liver postmitochondrial supernatant. The supernatants were prepared from pooled livers of adult female BD-IV rats that received an ip injection of 3-methylcholanthrene (40 mg/kg) 2 days before they were killed. At concentrations up to 75 μ M, the mutagenicity of the non-K-region 3,4-dihydrodiol was more than ten fold higher than that of the other K-region and non-K-region dihydrodiols and more than threefold higher than that of the parent hydrocarbon. 1,1,1-Trichloropropene increased the microsome-mediated mutagenicity of 7-methylbenz(a)anthracene but did not alter that of the four related dihydrodiols. (28 refs.)

77-0812 Levamisole and Hamster Pouch Carcinogenesis. (Eng.) Eisenberg, E. (Dept. Oral Medicine Oral Pathology, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA 02115) Shklar, G. *Oral Surg* 43(4): 562-571; 1977.

A total of 25 female and male Syrian hamster (10 mo old) were evaluated for the influence of systemically administered levamisole on carcinogenesis of the buccal pouch mucosa. The left buccal pouch of the hamster was painted three times per week 0.5% 9,10-dimethyl-1,2-benzanthracene. After each painting, each animal was given approx 0.7 mg levamisole hydrochloride po by disposable pipette. The hamster began showing evidence of slight pathologic changes in the mucosa only at 13 wk. There was slight erythema and some raised lesions. At 15 wk, the erythema and raised lesions were somewhat more obvious. At 17 wk, small papillary tumors could be observed in several of the animals. Microscopically, at 11 wk, some evidence of dysplasia was noted in addition to hyperkeratotic foci. No carcinomas were seen. By 17 wk several small papillary epidermoid carcinomas were found. They were well-differentiated and noninvasive. In one of the five animals killed at 17 wk, there was extensive involvement of the pouch with a large, necrotic, invasive carcinoma, resembling those seen in control animals at 17 wk. The observed retardation of chemical carcinogenesis by levamisole offers some basis for the concept of a relationship between malignant tumors and impaired immunologic reactivity. (38 refs.)

77-0813 In Vitro Effects of Prolactin and Hydrocortisone on 7,12-DMBA-Induced Mammary Tumour and Virus-Induced Sarcoma in the Rat. (Eng.) Aspegren, K. (Dept. Surgery, Univ. Lund, S-221 85 Lund, Sweden) *Acta Pathol Microbiol Scand [A]* 85(1): 57-62; 1977.

The influence of prolactin (5 μ g/ml) and/or hydrocortisone (1 μ g/ml), on 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in Sprague-Dawley rats was assessed by organ culture. Mammary tumors (M1-M5) were induced in 50-day-old female rats by intragastric instillation of 20 mg DMBA in an oil suspension. In addition, two sarcomas (S1-S2), one induced by polyoma virus and one by adenovirus in female inbred Wistar rats and transplanted for 13 and 16 generations, respectively, were used. Three mammary tumors (M1, M4 and M5) and the sarcomas were actively growing and increased their DNA synthesis from days 3 to 5, mammary tumor M2 was fairly stationary, and M3 increased from days 3 to 4 and then decreased to its original level on day 5. The DNA synthesis of M4 was stimulated significantly by prolactin at all culture times. M3 was stimulated on day 5 only, and the remaining mammary tumors remained unaffected. S1 was significantly inhibited on days 4 and 5, and S2 was not affected. M1, M3, M4, and M5 were inhibited by hydrocortisone on day 4, and M1 and M4 were also inhibited on day 5. S1 was stimulated on days 3 and 4 but not on day 5, and S2 was stimulated on days 4 and 5. M2 and M5 were not affected by the combination of prolactin and hydrocortisone, but M1, M3, and M4 were inhibited on day 4 and M4 was also inhibited on day 5. S1 was stimulated at all culture times, S2 only on day 4. Control flasks and prolactin-treated flasks demonstrated healthy cells but no glandular arrangement. There was a central necrosis. However, hydrocortisone-treated flasks showed a very marked lobuloalveolar differentiation, and no central necrosis of the explant was visible. The addition of prolactin did not alter the histological picture in the two groups. There were, moreover, no significant differences in DNA synthesis among the various groups. (8 refs.)

77-0814 Metabolism and Cytotoxicity of 7,12-Dimethylbenz(a)anthracene by Hamster, Rat and Rabbit Embryo Cell Cultures. (Eng.) Gentil, A. (Institut de Recherches Scientifiques sur le Cancer, Boite Postale No. 8, 94800-Villejuif, France) Lasne, C.; Chouroulinkov, I. *Xenobiotica* 7(4): 221-233; 1977.

The metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) by rat, hamster, and rabbit fibroblasts and liver homogenates was studied. The fibroblasts from the three species metabolized DMBA to a variety of ethyl acetate-soluble hydroxymethylated derivatives, dihydrodiols, phenols, and unidentified, polar metabolites similar to those produced by liver preparations from the same species. The cells also converted the hydrocarbon to unidentified water-soluble derivatives, but not to the K-region glutathione conjugate produced by the liver homogenates. High yields of phenols and other more polar metabolites, which may be tetrahydrotetrols, were produced by rabbit fibroblasts. According to kinetic stu-

es, the metabolic activity of rabbit fibroblasts was high, but the conversion of DMBA into water-soluble metabolites was lower than that with hamster and rat fibroblasts. With the rat and hamster cells, cytotoxicity and conversion to water-soluble metabolites were identical, whereas with rabbit cells the conversion was lower and cytotoxicity greater. This indicates that cytotoxicity is related to ethyl acetate-soluble metabolites that are not converted to water-soluble ones. It would be interesting to know if these differences in metabolism are related to the fact that rabbit sc tissues do not easily develop sarcomas after the injection of polycyclic hydrocarbons, but hamster and rat sc tissues do. (30 refs.)

77-0815 **Chemiluminescence of Mouse Liver after Administration of a Carcinogen.** (Eng.) Bat'yanov, P. (Inst. General Pathology and Pathophysiology, Acad. Medical Sciences USSR, Moscow, USSR) *Bull Exp Biol Med* (10): 1556-1557; 1976.

Radiation from the mouse liver was studied in vivo in the early days after sc injection of 9,10-dimethyl-1,2-benzanthracene (0.5-0.7 mg in 0.5 ml sunflower oil) into the mice. The radiation intensity was nearly constant in the control mice (solvent only), but it changed with time in the experimental mice. The intensity fell sharply between days 5-9 after injection and increased considerably between days 10-15. These results plus those of previous investigations suggest that the small increase in emission on the first day (compared with controls) is due to penetration of carcinogen possessing chemiluminescence over a wide region of the spectrum into the liver cells. Besides luminescence, much of the excitation energy of the carcinogen molecules must be expended at the start of the chemical reactions that lead to the formation of metabolites specific for the process of malignant change. An increase in the scale of these chemical conversions may bring about a gradual lowering of the radiation intensity. The change in metabolism results in the formation and gradual accumulation of an endogenous carcinogen with chemiluminescence over a wide region of the spectrum, which causes an increase in radiation intensity by the 10th day. (9 refs.)

77-0816 **Liver as an Inhibitor of Breast Tumors in Rats.** (Spa. Eng.) Caesar, G. (University of Saskatchewan, Regina, Saskatchewan, S4S0A2, Canada) *Can Oncol (Madr)* 11(2): 187-191; 1976.

The effect of liver extracts from rats that died of old age on dimethylbenzanthracene (DMBA)-induced mammary tumors was studied. Mammary tumors were induced in 80 virgin Wistar rats with a single dose of 20 mg DMBA by intubation. An additional 40 rats were designated as controls. Five weeks after treatment, tumor development was determined. In 40 rats with 82 tumors were given therapy with liver extract. Each rat was given 0.5 ml of the liver extract sc once

a week for 3 wk. Another group of 40 rats with 79 tumors received no treatment. The 40 untreated rats lived from 350 to 400 days, and all succumbed to mammary cancer. The 40 control rats did not develop mammary cancer and lived from 650 to 710 days. The 40 rats treated with both DMBA and liver extract lived from 596 to 710 days, and 30 showed regression of their mammary tumors. The results suggest that the liver therapy stimulated remission of the mammary tumors. The nature of the agent or agents that caused the remission is unknown. (6 refs.)

77-0817 **Enzymic and Immunological Activities of Lymphocytes During Chemical Carcinogenesis.** (Eng.) Airapet'yan, G. P. (Res. Lab. Experimental Immunobiology, Acad. Medical Sciences USSR, USSR) Maiskii, I. N.; Gudkova, R. B.; Airapet'yan, L. K. *Exp Biol Med* 81(5): 738-740; 1976.

The immunological and enzymic activities of lymphocytes during chemical carcinogenesis are investigated. Dimethylbenzanthracene was injected im in a dose of 3 mg per animal into Wistar rats. Before treatment with the carcinogen and for 5 mo after its injection, the dynamics of activity of three enzymes was studied in the blood lymphocytes: succinate dehydrogenase (SD), α -glycerophosphate dehydrogenase (α -GPD), and acid phosphatase (AP). After 2 mo of carcinogenesis, when the immunodepressive action of the carcinogen was reduced, a significant decrease was observed in SD activity and an increase in AP activity. At this stage of carcinogenesis, 66% of the animals were producing one of the mediators of cellular antitumor immunity, for the macrophage migration inhibition index was 0.55. By the third mo of carcinogenesis, the level of all three enzymes was considerably reduced. This decrease in enzymic activity of the lymphocytes had already started after 2.5 mo. Low dehydrogenase activity was linked with increasing severity of the pathological process. The macrophage migration inhibition index remained at its previous level, but this test was positive in only 58% of animals. By 4 mo, the inhibition index remained high (0.53) in only 36% of rats. Changes in the enzymic status of the lymphocytes during carcinogenesis were revealed by correlation analysis. Before administration of the carcinogen, moderate positive correlation was found between the activity of the dehydrogenases, and the coefficient of correlation was 0.40. After 2 mo of carcinogenesis, correlation between them was now negative, confirming a compensatory increase in α -GPD activity associated with a decrease in SD activity. The disturbance of the energy balance of the lymphocytes was confirmed by determination of correlation between the activities of each of the enzymes and this index under normal conditions. Between the 3rd and 4th mo of carcinogenesis, the rates of increase of SD and AP activity did not differ significantly from their decrease in the previous time interval. The rate of rise of α -GPD activity was more than three-fold greater than the rate of its decrease between the 2nd and 3rd mo. In the later stages of carcinogenesis, there is a disturbance of lymphocyte enzyme metabolism. (12 refs.)

- 77-0818 **Structure-Carcinogenic Activity Relationships in the Benz[a]anthracene Series. 1,7,12- and 2,7,12-Trimethylbenz[a]anthracenes.** (Eng.) Newman, M. S. (Dept. Chemistry, Ohio State Univ., Columbus, OH 43210) *J Med Chem* 20(1): 179-181; 1977.

The syntheses of 1,7,12-trimethylbenz(a)anthracenes and 2,7,12-trimethylbenz(a)anthracenes (I and II) are described. The starting materials for I and II were 1,12-dimethyl-7-iodomethylbenz[a]anthracene and 2-carbomethoxy-7,12-dimethylbenz[a]anthracene, respectively. Groups of 18 male CD random-bred rats received single sc injections of 0.75 or 1.5 mg of 7,12-dimethylbenz(a)anthracene (DMBA) or 0.5 mg of I in the right hind leg. None of the rats injected with I developed tumors. However, by 6, 10, and 15 mo, 4, 8, and 14, respectively, of the rats injected with the lower dose of DMBA and 7, 17, and 17, respectively, of the rats injected with the higher dose had developed sarcomas at the injection site. In another experiment, groups of 12 male Fischer rats received one sc injection in the right hind leg of 2.2 mg of DMBA or 2.3 mg of II one or three times at weekly intervals. All 12 rats in each of the two groups injected with II survived 18 mo and were tumor-free on autopsy. Of the DMBA rats, five had sarcomas at the injection site by 6 mo and all had sarcomas at the injection site by 8 mo. (18 refs.)

- 77-0819 **The Relationship Between Carcinogenic Activities of Polycyclic Aromatic Hydrocarbons and Their Singlet, Triplet, and Singlet-Triplet Splitting Energies and Phosphorescence Lifetimes.** (Eng.) Morgan, D. D. (Medical Res., 151, Veterans Admin. Hosp., 3200 Vine St., Cincinnati, OH 45220) Warshawsky, D.; Atkinson, T. *Photochem Photobiol* 25(1): 31-38; 1977.

The energies of the lowest excited singlet (E_s) and triplet (E_t) states and singlet-triplet splitting energies ($\Delta E_{s,t}$) of polycyclic aromatic hydrocarbons were examined. The energies were determined for 49 different polycyclic aromatic ring systems from the 0-0 band in their fluorescence and phosphorescence emission spectra, respectively. Phosphorescence lifetimes were obtained on 45 of these compounds using a computer-assisted technique. All values were also determined for a family of compounds, the methyl-substituted benz(a)anthracenes. The compounds were divided into 18 carcinogens and 31 noncarcinogens on the basis of animal test data. The results demonstrated that E_s values were strongly correlated with carcinogenicity, but E_t , $\Delta E_{s,t}$, and phosphorescence lifetime values were not. When E_t or $\Delta E_{s,t}$ were plotted as a function of E_s , the carcinogens tended to group in a cluster whose boundaries were represented by an ellipse. The E_s , E_t ellipse had foci (E_s , E_t) at 280.3, 173.6 and 322.2, 232.2 kilojoules (kJ)/mole and a principal axis equal to 86.2 kJ/mole. Similarly, the E_s , $\Delta E_{s,t}$ ellipse had foci (E_s , $\Delta E_{s,t}$) at 285.8, 112.1 and 331.4, 82.4 kJ/mole and a principal axis equal to 72.8 kJ/mole. The ellipse in each case was the one that gave the best correlation with carcinogenic activity. Either some property of the lowest excited singlet state, but not its energy,

or some molecular property that runs parallel to singlet-state energies may be significant in determining carcinogenic activity in polycyclic aromatics. (70 refs.)

- 77-0820 **The Photodynamic Immobilization of *Artemia Salina* Nauplii by Polycyclic Aromatic Hydrocarbons and Its Relationship to Carcinogenic Activity.** (Eng) Morgan, D. D. (Medical Res., 151, Veterans Admin. Hosp. 3200 Vine St., Cincinnati, OH 45220) *Photochem Photobiol* 25(1): 39-46; 1977.

The photosensitized immobilization of the nauplii of the crustacean *Artemia salina* was measured as a function of irradiation time and the amount of light absorbed by the sensitizer. Samples containing 30 *A. salina* nauplii in 2 ml of a sensitized salt water soln were irradiated at 366 nanometers. At least five sample tubes were run in parallel for each sensitizer, and the av number of nauplii immobilized per sample was measured as a function of irradiation time. Nauplii immobilization was preceded by an induction period, the length of which depended on the light intensity incident on the nauplii and the amount of light absorbed by the sensitizer. Once immobilization had begun, there was a linear relationship between the av number of nauplii immobilized and irradiation time. Nauplii aged an av of 24 and 48 hr were irradiated in identical soln of benz(c)acridine. The 48-hr-old nauplii were immobilized seven times faster than the 24-hr-old nauplii. Samples of 48-hr-old nauplii were incubated in the dark with benz(c)acridine soln for 0.5 to 22 hr and then irradiated. The relative photodynamic activity (RPA) reached a max after 2-3 hr dark incubation and was only slightly lowered after 22 hr. The RPA's of 41 different polycyclic aromatic hydrocarbons (19 carcinogenic and 22 noncarcinogenic) were determined using San Francisco Bay nauplii (av age 48 hr) following 2-hr dark incubation with an appropriate sensitizer. RPA were also assessed on 16/41 compounds following a 22-hr dark incubation. The relationships between carcinogenicity and RPA based on dark incubation period and the number of fused rings were analyzed. High RPA was restricted to carcinogenic compounds with four and five fused rings. Compounds with six or more fused rings had a low RPA regardless of carcinogenicity. There was an excellent correlation of RPA with carcinogenicity. Carcinogenesis by polycyclic aromatics may result from sublethal photodynamic effects. (10 refs.)

- 77-0821 **In Vitro Induction of Aryl Hydrocarbon Hydroxylase in Human Pulmonary Alveolar Macrophages by Benzantracene.** (Eng.) McLemore, T. L. (Dept. Medicine, Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX 77030) Martin, R. R. *Cancer Lett (Amsterdam)* 2(6): 327-333; 1977.

The induction of aryl hydrocarbon hydroxylase in human pulmonary alveolar macrophages (PAM) was examined

ht of its role in the formation of carcinogenic intermediates from aromatic hydrocarbons found in cigarette smoke. Cells were obtained from 8 nonsmokers and 10 smokers. The cells were cultured with benzantracene (BA) as the inducer, and the enzyme was measured fluorometrically. Optimum induction occurred with 10 μ M of BA and was complete after 24 hr. Enzyme levels remained constant through 48 hr and declined after 72 hr. The effects of different culture media were studied, and, in contrast to lymphocytes, the presence of mitogens was not required for induction. The effects of short-term culture (24 hr) on the enzyme activity were found to be negligible, and activity remained significantly higher among the smokers. When PAM from both groups were cultured with 10 μ M of BA for 24 hr, induced values of the enzyme were over 3 times higher than the noninduced values in smokers and over four times higher than the noninduced values in nonsmokers. Time and dose-response curves were established for the induction. Varying degrees of induction were observed when differing BA concentrations were used, up to a maximum at 10 μ M. The good correlation between freshly obtained PAM and cultured cells with regard to enzyme activity recommends the comparative use of macrophages and lymphocytes (which lack this correlation) to study the specific mechanisms involved in carcinogenesis. (8 refs.)

0822 **Metabolism of the Carcinogenic Hydrocarbon Benzo(a)pyrene in Human Fibroblast and Epithelial Cells. II. Differences in Metabolism to Water-soluble Products and Aryl Hydrocarbon Hydroxylase Activity.** (Eng.) Yamasaki, H. (Dept. Genetics, Weizmann Inst. Rehovoth, Israel) Huberman, E.; Sachs, L. *Int J Cancer* 19(3): 378-382; 1977.

l hydrocarbon (benzo(a)pyrene) hydroxylase (AHH) activity and the metabolism of benzo(a)pyrene (BP) to water-soluble products were measured in cultures of body fibroblasts and kidney epithelial cells from human embryos. Out of 8 different embryos, the highest metabolism of BP was found in fibroblasts from embryo No. 13, which metabolized 10 picomoles BP/10⁶ cells/3 days. The lowest metabolism of BP was found in fibroblasts from embryo No. 7, which metabolized 5.5 times less BP than those from embryo No. 13. AHH activity was measured in body fibroblast and kidney epithelial cell cultures from 23 different human embryos, of which 15 were also tested for metabolism of BP into water-soluble products. Enzyme activity was determined 24 hr after treatment with or without benzo(a)anthracene. The body fibroblasts from the different embryos could be divided into three groups, according to the amount of water-soluble products, but not according to AHH activity. The three groups were not noted in the cultures of kidney epithelial cells by the same assay. High metabolism to water-soluble products is not necessarily associated with high AHH activity in both epithelial cells and fibroblasts. (11 refs.)

77-0823 **Aryl-Hydrocarbon Hydroxylase Activity in Lymphocytes from Lung Cancer Patients and Normal Controls.** (Eng.) Guirgis, H. A. (Creighton Univ., Dept. Preventive Medicine Public Health, Criss III, Room 161, 2500 California St., Omaha, NB 68178) Lynch, H. T.; Mate, T.; Harris, R. E.; Wells, I.; Caha, L.; Anderson, J.; Maloney, K.; Rankin, L. *Oncology* 33(3): 105-109; 1976.

The activity of arylhydrocarbon hydroxylase (AHH) in lymphocytes from 11 normal controls (aged 35-77 yr) and 11 lung cancer patients (aged 46-73 yr) was evaluated. Variation in AHH activity among subsamples within individuals comprised 14.8% and 6.8% of the total variation among controls and lung patients, respectively. Coefficients of variation for AHH activity were similar in the two groups (28.7% for controls and 33.1% for the patients). The patients exhibited more variation in AHH activity than the controls. Furthermore, the av AHH activity of the patients was almost four times that of the controls. Similar results were obtained from comparisons made between the eight cigarette smokers of the controls and age-matched lung cancer patients: the cancer patients exhibited much more variability and a significantly higher av level of AHH activity. AHH activity expressed as the amount of water-soluble forms of benz(a)pyrene produced per 8 hr/10⁶ cells and per μ g of DNA (AHH/DNA) was similar. The patients demonstrated much greater variation in AHH/DNA than controls, and the av level was higher in the lung cancer group. These results could not be ascribed to differences in DNA content, because the av level of DNA in both groups was the same. Furthermore, there was a strong positive correlation between AHH and AHH/DNA in the cancer and control groups, respectively. However, the correlations between DNA and AHH or AHH/DNA did not approach statistical significance. Although there was no significant difference in the proportion of T and B cells between lung cancer patients and controls, the data reflect a smaller proportion of T cells among the patients. (19 refs.)

77-0824 **Correlation Between Tumor Growth and Protein Variations in Interstitial Liquid and Serum.** (Fre.) Vaillier, D. (Unite de Cancerologie Experimentale et de Radiobiologie, INSERM, U. 95, Plateau de Brabois, 54500 Vandoeuvre-les-Nancy, France) *Ann Immunol (Paris)* 128C: 117-119; 1977.

Experiments in mice have shown that tumor cells in diffusion chambers implanted adjacent to chemically induced tumors will grow faster than cells in chambers at a distance from the tumors. The interstitial fluid and serum of mice bearing "stimulating" tumors (Rous sarcoma virus- or 3-methylcholanthrene-induced) were studied by polyacrylamide gel electrophoresis. A significant decrease in β -lipoproteins, transferrin, and α -globulins was observed in the interstitial fluid. No alterations from normal were observed in the proteins of the serum. (5 refs.)

- 77-0825 Carcinogenesis Induced by Polycyclic Aromatic Hydrocarbons in Male and Female (CBA × C57/BL)F₁ Mice.** (Eng.) Finogenova, M. A. (Lab. Carcinogens, Inst. Nutrition, Acad. Medical Sciences USSR, Moscow, USSR) *Bull Exp Biol Med* 82(10): 1554-1555; 1976.

The effects of sex differences on the frequency of skin tumors induced by polycyclic aromatic hydrocarbons in hybrid (CBA × C57/BL) mice were investigated. The carcinogens used were 3-methylcholanthrene (3-MC) and benz(a)pyrene (BP). Three series of experiments were performed: (1) 0.02 ml 3-MC was applied to the skin daily until the appearance of malignant tumors; (2) 0.02 ml 3-MC was applied once, followed 2 wk later by croton oil in benzene once a week until the 20th week; (3) 0.02 ml BP was applied weekly until the 24th week. In all three experiments, the latent period for development of papillomas was shorter and the number of papillomas was higher in male than in female mice. The results indicate that sex differences exist in the development of skin tumors induced by polycyclic aromatic hydrocarbons in mice. (4 refs.)

- 77-0826 Carcinogenic Polycyclic Aromatic Hydrocarbons in Petroleum Products. Possible Prevention of Mineral Oil Cancer.** (Fre.) Thony, C. (Centre de Medecine du Travail de Cluses, B.P. no. 113, 74302 Cluses, France) Thony, J.; Lafontaine, M.; Limasset, J. C. *INSERM Symposia Series* 52: 165-170; 1976.

The incidence of cancer in machine-finishing workers in the Cluse area was surveyed. The metal-machinery industry employs 6,500 people, 5,000 of whom are exposed to petroleum products by direct cutaneous contact, by impregnation of their work clothes, or by standing in the aerosols produced by the machines. Over a 15-yr period (1960-1974), 133 cases of spinocellular epithelioma were registered, 63% of the scrotum, 30% of the forearm and hands, and, more rarely, the face and neck. Precancerous cutaneous lesions such as papillomas and keratoacanthomas were seen frequently. Particularly disturbing was the incidence of scrotal cancer: 330/100,000 machine-finishing employees compared to 25/100,000 of the general population. The concentration of benzo(a)pyrene (BP) in the oils used to manufacture metal machinery is tabulated. New oil contains 0.5-150 µg/liter of BP, and used oils contain higher concentrations of carcinogenic hydrocarbons. Refining the oil to eliminate or chemically transform the aromatic hydrocarbon fraction is strongly recommended. (no refs.)

- 77-0827 Investigations on the Carcinogenic Burden by Air Pollution in Man. XIV. Effects of Automobile Exhaust Condensate on the Syrian Golden Hamster Lung.** (Eng.) Mohr, U. (Abteilung für Experimentelle Pa-

thologie, Medizinische Hochschule, Karl-Wiechert-Allee D-3000 Hannover 61, W. Germany) *Zentralbl Bakteri [Orig B]* 163(5/6): 425-432; 1976.

The effects of automobile exhaust condensate on the Syrian golden hamster lung were investigated. Groups of six 12-v old male hamsters were intratracheally instilled with either 5 mg/animal (containing 1.7 µg benzo(a)pyrene [BaP]) or 2 mg/animal (0.85 µg BaP) of automobile exhaust condensate at 2-wk intervals. A third group of six animals served as control. All animals were sacrificed between wk 30 and 40 of treatment and received between 15 and 30 instillations. The smallest total dose of BaP in the higher dosage group was 25.50 µg and that in the lower dosage group was 11.1 µg BaP. All of the animals developed multiple pulmonary adenomas. The neoplasms frequently originated from segmental bronchi or peripheral bronchioles. In addition to the adenomas, numerous polyploid hyperplastic areas were observed in lobar and segmental bronchi. The peripheral lung tissues were crowded with condensate-laden macrophages which occasionally contained a few granulocytes. Known carcinogenic polyaromatic hydrocarbons in the automobile exhaust condensate included, in addition to BaP (340 µg/g), the following: benzo(a)anthracene (280 µg/g), chrysene (40 µg/g), benzo(b)fluoranthene (162 µg/g), benzo(j)fluoranthene (94 µg/g), dibenz(a,h)anthracene (96 µg/g), and indeno(1,2,3-cd)pyrene (268 µg/g). It thus appears that automobile exhaust condensate displays a carcinogenic effect on Syrian golden hamster lungs. Considering the relatively low total dose of BaP contained in the condensate, this pronounced neoplastic response cannot be explained by the effects of BaP alone. (12 refs.)

- 77-0828 Techniques for Localized Injections and Topical Applications of Carcinogens at Specific Endobronchial Sites in Dogs.** (Eng.) Okita, M. (Pulmonary Cancer Inst. Chiba Univ., Chiba, Japan) Benfield, J. R.; Jensen, Matsumura, K.; Shors, E.; Cohen, A. *J Thorac Cardiovasc Surg* 73(2): 216-220; 1977.

To create a practical canine model for the induction of specifically localized lung cancers analogous to human bronchogenic carcinoma, techniques for recurrent topical applications and endobronchial transbronchoscopic submucosal injections of carcinogens, with subsequent biopsies, have been developed. Following 2 yr experience with 2,868 endoscopic manipulations in 59 dogs, effective techniques for administering various dosages of 3,4-benzo(a)pyrene (BP) and nitroso-N-methylurea (NMU) have been refined. The methods and instruments used are described. Complications and deaths occurred during 49 endoscopies (1.7%). There were 5 exsanguinations, 5 anesthetic deaths, and 39 nonlethal episodes of serious bleeding after brushings or biopsies with mm punches, mainly in immunosuppressed animals or those having local irritation. All lethal hemorrhages following biopsies occurred at the site of carcinogenesis. Preneoplastic endobronchial changes were safely induced by submucosal

injections of either 15 mg/wk of BP or 10 mg/wk of NMU. Topical applications of 10 mg/wk NMU to prepared sites enhanced the friability of the mucosa. (11 refs.)

77-0829 Metabolites of Benzo(a)pyrene Produced by Placental Microsomes from Cigarette Smokers and Nonsmokers. (Eng.) Wang, I. Y. (Dept. Basic and Clinical Immunology and Microbiology, Medical Univ. South Carolina, Charleston, SC 29401) Rasmussen, R. E.; Creasey, J.; Crocker, T. T. *Lif Sci* 20(7): 1265-1272; 1977.

The metabolism of tritiated benzo(a)pyrene (³H-BP) was studied in vitro in the microsomes obtained from the human placentas of 6 smokers and 11 nonsmokers. In a preliminary study, it was shown that the microsomal fraction (100,000 × g pellet) had the highest ³H-BP-metabolizing activity (40% of total activity) per mg protein; the 900 × g pellet had about 10% of the total specific activity, and the 10,000 × g pellet, about 35%. One professed nonsmoker yielded a preparation that metabolized ³H-BP at a rate similar to that of the smokers. All smokers had high ³H-BP metabolizing activity in their microsomal preparations. Cigarette smoking during pregnancy induced placental enzymes which converted benzo(a)pyrene (BP) to a variety of metabolites. The major metabolite was 3-hydroxy-BP (3-OH-BP). The av amount, in picomoles, of this group of metabolites was 132-288 in placental microsomes from six subjects who smoked 2-20 cigarettes/day during pregnancy compared to 3.4 in nonsmokers. The yield of 7,8-dihydrodihydroxy-BP was 13%-20% of that of 3-OH-BP. Other metabolites included 9,10-dihydrodihydroxy-BP, 4,5-dihydrodihydroxy-BP, quinones BP and unidentified metabolites which were more polar than the diols. This study shows that cigarette smoking induces enzymes in the human placenta, which convert a known carcinogen to several derivatives. (34 refs.)

77-0830 Liver Tumors Induced by 4-Dimethylaminoazobenzene: Experimental Basis for a Chemical Carcinogenesis Concept. (Eng.) Anghileri, L. (Klinikum der Universität Esse-Gesamthochschule, Innere Klinik und Poliklinik (Tumorforschung), D-4300 Essen, Aufelandstr. 55, W. Germany) Heibredner, M.; Weiler, G.; Hermietzel, R. *Arch Geschwulstforsch* 46(8): 639-656; 1976.

Liver tumors induced by 4-dimethylaminoazobenzene (DAB) were investigated in male Wistar rats. Groups of rats were fed (ad libitum) a basal semisynthetic diet supplemented with 0.06% DAB; some were also given B vitamins in water by pipette. In rats given vitamins, only a small increase by 10% of the tumor induction period was found. Approx 27% of the animals sacrificed after 7 mo of DAB feeding presented macroscopically discernible tumors. Before the first tumor was observed, the livers of rats given vitamins had a significant increase of Ca and an increase of Na. After 7 mo of DAB on the diet, the Mg and Ca contents decreased; there was also

a slight decrease in K and Na. At the end of 18 mo, the percentage of rats with tumors was higher (70%), and the liver tissue showed a decrease of Mg and Ca but an increase of K and Na. In the absence of vitamins, lower liver Mg and Ca was accompanied by increased Na during the period before tumor onset. The subcellular distribution studies indicated that after 7 mo, the developed tumor showed an increase of Ca in all the subcellular fractions; it was especially high in nuclear and mitochondrial fractions. Livers without tumors had increases of Ca only in the mitochondria. Histological examinations showed that in rats after 1.5 mo of DAB without vitamins, the liver demonstrated polymorphism, polychromasia, hyperchromasia, and increased nuclear activity. After 2 mo, cholangiocarcinoma cells developed and started an invasive growth, with infiltration of the periportal region accompanied by strong fibrosis. The hepatomas showed a slower growth rate than the cholangiocarcinoma; in those appearing after 7 mo, there were signs of necrosis, cirrhosis, and regressive changes. It is postulated that the transformation produced by DAB is caused by an irreversible change of the cell membrane permeability that is provoked by interaction of the carcinogen with the cell membrane. (56 refs.)

77-0831 Influence of Riboflavin Antagonists on Azo Dye Hepatoma Induction in the Rat. (Eng.) Lambouy, J. P. (Dept. Biochemistry, Sch. Dentistry, Univ. Maryland, Baltimore, MD 21201) *Proc Soc Exp Biol Med* 153(3): 532-535; 1976.

The effect of riboflavin antagonists on azo dye hepatoma induction in Sprague-Dawley rats was studied. Feeding a diet containing 2 mg/kg riboflavin and 1 mmole/kg 3'-methyl-4-dimethylaminoazobenzene to rats for 18 wk protected the livers against hepatoma formation to the extent that 80% were normal. When the riboflavin antagonist flavin D (10.2 mg/kg) was added, the beneficial effect of the riboflavin was suppressed--80% of the animals developed hepatomas and 20% demonstrated precancerous conditions. When 10 mg/kg flavin E, a flavin possessing vitaminlike and antagonistic properties, was added, 30% of the rats died between weeks 3 and 8. None of the animals that died possessed hepatomas at the time of death. Only 25% of the livers of this group were normal, but 45% demonstrated hepatomas (35%) or precancerous lesions (10%). When the quantity of flavin E was reduced to 5.0 mg/kg, all the rats survived. Only 11% developed hepatomas, but the remaining 89% presented a gross appearance of livers not previously observed. The cirrhosis was severe but not unfamiliar, consisting of an orange-peel-like surface, with deep segmentation and notching of the edges of all lobes. All lobes appeared puffed. The striking difference was the presence of very diffuse, very blanched, whitish areas of the livers. The larger lobes, the median lobe, and the right and left lateral lobes in some cases showed half of their surfaces to be blanched. When animals were fed the basic diet to which flavin F (which has a side chain at position

10 other than D-ribityl) was added, the livers of all were normal. Flavin F may possess strong vitaminlike properties or it may be capable of protecting the liver against the effects of the carcinogen. (17 refs.)

- 77-0832 Diurnal Rhythms of Cell Proliferation in the Early Stages of Liver Carcinogenesis Induced in Mice by Orthoaminoazotoluene.** (Eng.) Mustafin, A. G. (Dept. General Biology, N. I. Pirogov Second Moscow Medical Inst., Moscow, USSR) *Bull Exp Biol Med* 82(7): 1066-1068; 1976.

The diurnal dynamics of DNA-synthesizing cells and of dividing hepatocytes in the early stages of carcinogenesis were investigated by autoradiography. Orthoaminoazotoluene (OAAT: 0.1 ml of 1% soln, 3 \times /wk) was injected into randomly bred male mice (av wt of 20-25 g) through the mouth directly into the esophagus from a syringe. The mice of Group 1 received OAAT for 1 mo (total dose 12 mg/animal), those of Group 2 for 5 mo (total dose 60 mg); Group 3 formed the controls. The mice were killed on the third day after the end of OAAT administration. ^3H -thymidine (0.5 $\mu\text{Ci/g}$ body wt) was given 1 hr before sacrifice. One mo after the start of OAAT, the normal pattern of the liver structure was lost because of the proliferation of oval cells. Marked polymorphism of the liver cells was noted. Greatly enlarged liver cells with large hyperchromic nuclei were observed occasionally. Multiple foci consisting of small homogeneous, and usually basophilic cells, with round nuclei containing one or two nucleoli, appeared in the liver parenchyma of Group 2. The diurnal rhythm of the index of labeled nuclei (ILN) of the hepatocytes in Group 1 mice was monophasic, with a max at 7 p.m. and a minimum at 10 p.m. to 7 a.m. There was a phase shift of 3 hr in the rhythm relative to the max for controls. In Group 2 mice, the diurnal rhythm of the DNA-synthesizing cells began to exhibit two ILN max, at 4 p.m. and 4 a.m. Diurnal changes in the mitotic index (MI) of the hepatocytes in the second stage of carcinogenesis were analogous to the changes in the controls. The ILN max was observed 12 hr before the MI max. Comparison of the av diurnal values of ILN and MI in the experimental and control series demonstrated that following administration of OAAT for 1 mo, there was a decrease in the av diurnal values of MI and ILN. The av diurnal values of MI and ILN were more than twice as high as in the earlier stage of carcinogenesis. The existence of a diurnal rhythm is evidence of partial preservation of liver cell sensitivity. (11 refs.)

- 77-0833 Diurnal Rhythms of Cell Proliferation in Late Precancerous Changes Induced in the Liver by Orthoaminoazotoluene.** (Eng.) Mustafin, A. G. (Dept. Biology, N. I. Pirogov Second Moscow Medical Inst., Moscow, USSR) *Bull Exp Biol Med* 82(10): 1551-1553; 1976.

The diurnal rhythms of mitotic activity and the number of DNA synthesizing cells were studied by autoradiography with ^3H -thymidine in male mice that had been given the liver carcinogen orthoaminoazotoluene by direct injection into the esophagus 3 \times /wk for 9 mo (total dose, 120 mg/mouse). In Stages II (adenomatous nodules) and III (primary hepatomas) of carcinogenesis, a monomodal rhythm of mitotic activity was demonstrated in the developing tumors and in the surrounding liver parenchyma; the number of mitoses reached a max at 4-7 a.m. The diurnal rhythm of the number of labeled nuclei was bimodal, with maxima at 7 p.m. and 4 a.m. The mean diurnal values of both indices at Stages I and III of hepatocarcinogenesis were higher than those for the surrounding noncancerous liver tissue. The results indicate that a diurnal rhythm of cell reproduction is typical of tumor growth both in the initial and later stages of tumor development. (16 refs.)

- 77-0834 Transplacental and Direct Action of Orthoaminoazotoluene of Organ Cultures of Embryonic Mouse Liver.** (Eng.) Kolesnichenko, T. S. (Dept. Study Carcinogenic Agents, Oncologic Scientific Center Acad. Medical Sciences USSR, Moscow, USSR) Popova, N. V. *Bull Exp Biol Med* 82(9): 1399-1402; 1976.

Marked differences in the direct and transplacental action of orthoaminoazotoluene (OAAT) on CBA-mouse embryonic liver are reported. The direct action was studied in culture to which 0.001 mg/ml of OAAT was added and the removed after 3-4 days. In such cultures there was a marked decrease in survival of the organ cultures compared to cultures from the livers of control mice. In the study of transplacental action, mice received a total of 24 mg of OAAT, starting on day 16 of pregnancy, with explantation of the embryonic livers after 19-20 days of pregnancy. When OAAT acted via the placenta, its toxic effect was replaced in the later stages of cultivation by a growth-stimulating effect, which was especially marked after 23-24 days of cultivation. At that time among 35 explants studied, 15 were viable compared to 8/74 from the controls. (9 refs.)

- 77-0835 Production of Intestinal and Other Tumours by 1,2-Dimethylhydrazine Dihydrochloride in Mice. II. Scanning Electron Microscopic and Cytochemical Study of Colonic Neoplasms.** (Eng.) Toth, B. (Eppley Ins. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE 68105) *Br J Exp Pathol* 57(6): 696-705; 1976.

The three-dimensional surface structures of normal colonic epithelium and of neoplastic colonic epithelium induced by 10 weekly sc injections of 20 $\mu\text{g/g}$ body wt 1,2-dimethylhydrazine dihydrochloride (1,2-DMH) in Swiss albino mice were assessed by scanning electron microscopy.

the surface composition of these were evaluated by ultrastructural cytochemistry. In the colons of the treated animals, single or multiple nodular tumors protruding into the luminal space were seen. The adenocarcinomas demonstrated a complete change of the mucosal surface topography. Cell surfaces in adenocarcinomas departed radically from the usual polypoidal shape and were highly variable in size. The malignant epithelial cell luminal surface displayed a distinctive asymmetry. Variations in cell size and contour resulted in the formation of irregular elevations and depressions in the epithelial topography. The absorptive cells that occupied the intercrypt regions protruded into the lumen. The short blunt microvilli of the neoplastic cells were larger in diameter than their normal counterparts, they were club-shaped, and they were arranged asymmetrically. The ruthenium red reaction product occurred as a homogeneous deposit or in the form of fine granules on the external surface of absorptive cell microvilli. The distribution and quantity of staining material was uniform along the surface of normal luminal colon cells, but it varied from cell to cell in the neoplastic epithelium. Similar results were noted for nucleotide phosphatase activity, using ATP as substrate. In the adenocarcinomas, differential staining was often present on adjacent cells. The sparse number of microvilli on some cells correlated with decreased ATPase activity and mucopolysaccharide content. (27 refs.)

77-0836 **Species Variation in Response to Dimethylhydrazine.** (Eng.) Wilson, R. B. (Dept. Veterinary Microbiology and Pathology, Washington State Univ., Pullman, WA 99163) *Toxicol Appl Pharmacol* 38(3): 647-650; 1976.

Species variation in response to 1,2-dimethylhydrazine dihydrochloride (DMH) is investigated. DMH was administered intragastrically (ig) or sc to miniature swine (60 or 30 mg/kg), dogs (60, 30, 15, or 5 mg/kg), and guinea pigs (60 or 30 mg/kg). Tumors were not noted in any swine. Only three of eight animals from Group 1 (60 mg/kg, ig) survived longer than 10 wk. All others died or were killed in a moribund condition between the 4th and 9th wk. Hemorrhagic, hepatic degeneration, and necrosis were observed in all swine. Icterus, bile duct proliferation, and megalocytosis were common findings. Massive hemorrhage into the gut occurred in three animals. All animals in Group 2 (60 mg/kg, sc) died and were killed in a moribund condition between 4 and 8 wk. Lesions and signs were similar to those found in animals of Group 1. One swine in each of Groups 3 and 4 (30 mg/kg, ig) became moribund and was killed during the seventh wk. Local megalocytosis and postnecrotic fibrosis were observed in the livers of surviving swine at 18 mo. Tumors were not found in any dogs. All animals in Groups 6, 7, and 8 (60 or 30 mg/kg, ig or 60 mg/kg, sc) died during the second wk. They had developed icterus and had lost significant wt. Hepatic degeneration and hemorrhagic necrosis were observed in each. Karyolytic changes were common in hepato-

cytes. One dog in Group 9 (15 mg/kg, ig) lived 1 mo after the eighth and final dose of DMH; all other four dogs, and all of those in Group 10 (15 mg/kg, sc), died between wk 4 and 8. All had signs and lesions of hepatic failure. All animals in Groups 11 and 12 (5 mg/kg, ig or sc) survived 10 weekly doses of DMH, but suffered transitory toxic signs, including loss of appetite and icterus. Signs of toxicity in guinea pigs of Groups 14 and 15 (60 mg/kg, ig or sc) included reduction in food intake and stunted growth. Only one of six animals from each group survived 8 mo. Both were killed in a moribund condition. Each had developed bile duct carcinoma with invasion to the pancreas, peritoneum, spleen, and metastases to the lungs. All animals in Groups 16 and 17 (30 mg/kg, ig) survived to 11 mo, but during the next 7 mo, all were killed in a moribund condition. Hepatomas were found in two of six animals in each group. Bile duct cell carcinomas had developed in five animals in Group 16 and four in Group 17. Differences in DMH metabolism exist among various species. (11 refs.)

77-0837 **Inhibition of 1,2-Dimethylhydrazine Metabolism by Disulfiram.** (Eng.) Fiala, E. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595) Bobotas, G.; Kulakis, C.; Weisburger, J. H. *Xenobiotica* 7(1/2): 5-9; 1977.

The effects of disulfiram on the metabolism of 1,2-dimethylhydrazine were studied in male CD Fischer rats. Disulfiram was administered by stomach tube, as a suspension of finely pulverized crystals in 4% aqueous starch at a level of 1 g/kg body wt. Controls received only starch. Two hr later, ¹⁴C-dimethylhydrazine was administered by sc injection at either 21 mg/kg or 200 mg/kg; the level of radioactivity was 4 to 9 μ Ci/animal. Disulfiram, at the lower dose, caused an increase of approx 150% in the amount of azomethane exhaled. At the higher dose, the increase was approx 27%; the amount of CO₂ exhaled decreased at both doses. There was no increase in ¹⁴C metabolites in the urine at either dose. High pressure liquid chromatography of the urine indicated that disulfiram caused a marked decrease in the quantity of urinary dimethylhydrazine metabolites. These results suggest that disulfiram blocks N-oxidation of azomethane to azoxymethane, thereby preventing the formation of CO₂. The accumulated azomethane is eliminated by respiration. The inhibition of metabolism to CO₂ indicates that electrophilic carbonium ion formation is blocked, resulting in inhibition of tumor formation. (12 refs.)

77-0838 **Effect of Pair-Feeding of Carcinogen on the Incidence of Bladder Tumors in Hamsters. Role of Indole, Age, and Sex.** (Eng.) Matsumoto, M. (Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL 60611) Hopp, M. L.; Oyasu, R. *Invest Urol* 14(3): 206-209; 1976.

The role of indole in 2-acetylaminofluorene (AAF) bladder tumorigenesis is studied in pair-fed Syrian golden hamsters. Hematuria was common after 6 mo of treatment, particularly in the animals fed the indole diet. Microscopically, this was associated with hyperplasia of the transitional cell epithelium and intraepithelial extension of capillaries from the lamina propria. The bladder tumor incidence rose stepwise, notably after 10 mo. In both males and females, the indole group developed a higher incidence. A significant difference in tumor incidence was noted between the two dietary groups in both males and females when all surviving animals were compared. A total of 22 of 45 male hamsters fed the combination diet and 14 of 53 male hamsters fed the diet containing AAF alone developed bladder tumors. Similarly, in the female groups, the incidence was 13 of 48 and 4 of 53, respectively. The role of indole in the earlier development of tumors was also specifically demonstrated when the incidence of tumors in animals (males and females) fed the combination diet was compared to that of the AAF diet at 8 and 12 mo. Also observed was a difference in susceptibility to bladder tumorigenesis in males and females. In both dietary groups, male animals developed more tumors than did females. In the hamsters treated with AAF alone, regenerated, or hyperplastic hepatic nodules, or both were common and were associated with varying degrees of cholangiofibrosis. In the presence of indole in the diet, such lesions were rare, but cystadenomatous proliferation was common. Three cholangiocarcinomas and one hepatoma found in female animals and two hepatomas found in male animals were all observed in the AAF group. Indole did not change the urinary output in males of N-hydroxy-2-acetylaminofluorene. The mechanism involved in the bladder tumor enhancement by indole is not clear. (21 refs.)

77-0839 Non-random Binding of a Chemical Carcinogen to the DNA in Chromatin. (Eng.) Metzger, G. (Univ. Texas at Dallas, P. O. Box 688, Richardson, TX 75080) Wilhelm, F. X.; Wilhelm, M. L. *Biochem Biophys Res Commun* 75(3): 703-710; 1977.

Adult male and female BD 4 rats received ip 2-acetylaminofluorene labelled with ^{14}C in position 9 (specific activity 26 Ci/mM). The rat liver nuclei were studied at intervals of 10 min to 72 hr after injection of 55 $\mu\text{Ci}/100\text{ g}$ body wt. The nuclei were collected by centrifugation and digested with Staphylococcal nuclease or pancreatic nuclease (DNase I). It was shown that the carcinogen is nonrandomly distributed along the DNA of chromatin since it binds preferentially to the regions of chromatin digested by the Staphylococcal nuclease; these regions are those resistant to DNase I. The percentage modification ($\times 10^4$) of digested and Staphylococcal nuclease resistant chromatin DNA after 10 min was 1.13 and 0.52, respectively; after 30 min 0.73 and 0.56, respectively; after 72 hr 5.70 and 4.09, respectively. The results also indicate that the two nucleases do not recognize exactly the same region of chromatin. (14 refs.)

77-0840 Mitotic Anomalies Induced by Three Inhalation Halogenated Anesthetics. (Eng.) Kusyk, C. J. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030) *Environ Res* 12(3): 366-370; 1976.

The mitotic anomalies induced by three inhalation halogenated anesthetics (halothane, methoxyflurane, and enflurane) are investigated in a human lymphoid cell line JC, two cactus mouse fibroblast lines, and 4-day-old chick embryos in vivo. The anesthetics caused an increased rate of mitotic anomalies. The abnormalities consisted of multipolar spindles, bridges and lagging chromosomes, unequal divisions, multinucleation, and degenerating mitotic figures. These abnormalities occurred with similar frequencies when the anesthetics were added directly to the medium or applied to the ceiling of the culture flasks. At a concentration of 0.1%, both halothane and enflurane caused up to more than 80% abnormal anaphases in 24-hr samples. Methoxyflurane caused similar abnormalities, but it appeared to be more toxic than the other two substances. At 0.1%, most cells were in the process of degeneration within 24 hr. Many cells died at mitosis with highly pycnotic chromatin bodies. The frequency of abnormal mitotic figures increased when the anesthetic concentration was increased or when the duration of exposure at the same concentration was lengthened. The frequencies of abnormal anaphases of cactus mouse cells steadily increased as the treatment time was prolonged, reaching approx 30% with both halothane (0.1%) and methoxyflurane (0.01%). The responses of the human lymphoid line JC to all three agents was almost the same. In another series of experiments, cell cultures were treated with each of the anesthetics for 24 hr and grown in the absence of the agents for an additional 24 hr. Preliminary results indicated that cellular recovery from the effects of the different anesthetics was not the same. In cultures originally treated with methoxyflurane and enflurane, the frequency of abnormal mitoses dropped to the control levels, whereas cells originally treated with halothane still exhibited a relatively high level of mitotic abnormalities. None of the anesthetics tested caused chromosome breakage or chromosome rearrangements. The data suggest that anesthetics share some cellular organelles as their action targets. (10 refs.)

77-0841 Methylene Chloride Passes Early Tests. (Eng.) Anonymous (No affiliation given) *Chem Eng News* 55(19): 6; 1977.

The possible use of methylene chloride as an aerosol propellant is discussed. The interim results of a 2-yr inhalation study involving nearly 2,000 animals indicate no evidence of cancer in test animals exposed to methylene chloride vapor. A variety of lesions were discovered in both control and exposed animals, but none were associated with exposure. Methylene chloride degrades rapidly in the lower atmosphere, does not generate photochemical oxidants, and is not

complicated in the ozone controversy. Problems involved with this compound are that it tends to hydrolyze, forming small amounts of hydrochloric acid, and that it metabolizes to carbon monoxide, which binds to Hb in blood. However, at permitted levels of exposure (500 ppm), methylene chloride elevates blood carbon monoxide slightly, if at all. (no refs.)

77-0842 **The Effects of Maternally Inhaled Vinyl Chloride on Embryonal and Fetal Development in Mice, Rats, and Rabbits.** (Eng.) John, J. A. (Toxicology Res. Lab. Health Environmental Res., Dow Chemical U.S.A., Midland, MI 48640) Smith, F. A.; Leong, B. K.; Schwetz, A. *Toxicol Appl Pharmacol* 39(3): 497-513; 1977.

Groups of pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to an atmosphere of gaseous vinyl chloride (VC: mice, 50 or 500 ppm; rats and rabbits, 500 or 2500 ppm) for 7 hr/day during the period of major organogenesis. Some animals were given 15% ethanol in their drinking water. Maternal toxicity was observed in all three species. Among the effects were: a decrease in maternal gain and in absolute liver wt and an increase in maternal deaths for mice exposed to 500 ppm VC; a decrease in maternal wt gain and an increase in liver wt for rats exposed to 500 and 2500 ppm VC, respectively; and a decrease in food consumption for all three species ($p < 0.05$ for all differences). VC alone did not cause consistent significant embryonal or fetal toxicity. Some decrease in fetal body wt and crown-rump length was observed in fetal mice and rats but not in rabbits. Inhalation of VC was not teratogenic in any of the species at the concentrations tested. Except for dilated ureters in litters of rats exposed to 2500 ppm VC, no external or soft tissue anomalies were observed at a significantly higher incidence than observed in the control animals. Examination of the fetal skeletons showed minor but no major skeletal variations in the VC groups. Ethanol treatment enhanced maternal toxicity more than embryo toxicity. (11 refs.)

77-0843 **Effect of Carbon Tetrachloride on RNA Metabolism in the Rat Liver.** (Eng.) Voronova, L. A. (Lab. Biochemistry Chemical Carcinogenic Agents, N. N. Petrov Res. Inst. Oncology, Ministry Health USSR, USSR) Ivanov, S. D.; Zabezhinskii, M. A. *Exp Biol Med* 81(5): 677-679; 1976.

The influence of carbon tetrachloride (CT) on RNA metabolism in the rat liver is studied. Noninbred male albino rats received CT by sc injections twice per wk in a dose of 1 ml/kg body wt. The analysis of the biochemical and morphological changes arising in the liver tissue revealed two principal stages of the process, the first of which corresponded to the time from 1-3 mo, and the second from 3-6 mo, after the beginning of administration of the agent. The first stage was characterized by fatty degeneration, necrosis of some hepatocytes, and proliferation of the epithelium of the small bile ducts.

There was a sharp increase in the intensity of incorporation of uridine-5- H^3 into RNA, cytoplasmic RNA, and nuclear RNA, followed by an equally sharp decrease. In the second stage, progressive proliferation of reticulum fibers became the predominant feature, with the appearance of collagen fibers and septal fibrosis. During this period, the intensity of incorporation of label into RNA and its fractions did not change as sharply as in the early stages of action of CT. The intensity of incorporation of label into RNA in the final stage of the process did not exceed the control, while the turnover of nuclear RNA was increased after exposures for 20 and 60 min. The RNA content in the liver tissue remained low, whereas the DNA content rose, so that the RNA/DNA ratio fell correspondingly. The cytoplasmic/nuclear RNA ratio was significantly increased at the beginning and end of the time of action of CT compared with the control, apparent evidence of a disturbance of the transport system characterizing the transfer of RNA from nucleus into cytoplasm. During the 1-3 mo period, there was a decrease in the content of RNA, nuclear RNA, and DNA, a decrease in the RNA/DNA ratio, and an increase in the cytoplasmic RNA/nuclear RNA ratio. The findings suggest that the sharply increased incorporation of labeled precursor into RNA of the liver during the first stage of the toxic action of CT reflects the compensatory character of changes in nucleic acid metabolism in that period aimed at restoring the disturbed equilibrium of metabolism. (10 refs.)

77-0844 **Sublethal Effects of a Pure Polychlorobiphenyl on Mice.** (Eng.) Carter, J. W. (Mid American Nazarene Coll., P.O. Box 1776, Olathe, KS 66061) Cameron, I. L. *Exp Mol Pathol* 26(2): 228-250; 1977.

The sublethal effects of the environmental contaminant 2,4,5,2',4',5'-hexachlorobiphenyl (PCB) were investigated in sexually mature, wt-stable male Swiss albino mice. The mice were given one dose of 0, 200, 500, or 1,000 mg PCB/kg po and then killed 28 days later. There was no change in food or water consumption or urine or fecal output during the 28 days. At the higher doses the kidney and spleen showed wt decreases. There was no change in gross body wt. A dose-dependent increase was observed in liver wt and content of PCB, accompanied by profound and well-defined histopathological changes of the centrilobular hepatocytes (CLH). The cell volume of the CLH of mice given 1,000 mg PCB/kg was three times that of untreated mice. Morphometric analysis of electron micrographs from each of 11 mice revealed that the number of lipid bodies and mitochondria per cell were significantly higher in the CLH treated with the 1,000-mg/kg dose. The membrane surface areas were also significantly elevated in the mitochondrial envelope, the mitochondrial cristae, and the smooth endoplasmic reticulum per CLH. The volumes of numerous cytoplasmic components were also significantly greater in the CLH treated with 1,000 mg PCB/kg. These components include the lipid bodies, secondary lyso-

somes, mitochondria, rough and smooth endoplasmic reticulum, and cytoplasmic fluid. (27 refs.)

- 77-0845 Isolation and Identification of Urinary Metabolites of AF-2 (3-(5-Nitro-2-furyl)-2-(2-furyl)acrylamide) in Rabbits.** (Eng.) Ou, T. (Faculty Pharmaceutical Sciences, Kyushu Univ., Fukuoka, Japan) Tsumi, K.; Yoshimura, H. *Biochem Biophys Res Commun* 75(2): 401-405; 1977.

Two metabolites isolated from the urine of adult male rabbits after a single po dose of ^{14}C -labeled 3-(5-nitro-2-furyl)-2-(2-furyl)acrylamide (AF-2: 0.27 $\mu\text{Ci}/\text{mg}$, 100 mg/kg as a suspension) are described. Chromatography of 24-hr urine samples in silica gel columns revealed a major (M-I) and a minor (M-II) metabolite. M-I, which consisted of yellow needles with a melting point of 117 C, is a new metabolite of a nitrofur derivative, 2-(β -carboxypropionyl)-3-(5-methylthio-2-furyl) acrylamide according to infrared, nuclear magnetic resonance, and mass spectroscopy. M-II, isolated as a yellow solid, appears to be a *cis-trans* isomer of M-I, based on UV and mass spectroscopy, and on its behavior on thin layer chromatography. (13 refs.)

- 77-0846 Mutagenic Effects of AF-2 a Food Additive, on Embryonic Cells of the Syrian Golden Hamster on Transplacental Application.** (Eng.) Inui, N. (Dept. Experimental Pathology, Cancer Inst., Japanese Foundation Cancer Res., Toshima-ku, Tokyo 170, Japan) Karetomi, M.; Nishi, Y. *Mutat Res* 41(2/3): 351-360; 1976.

The mutagenic effects of furylfuramide (AF-2) on embryonic cells of the Syrian golden hamster by transplacental application are evaluated. The hamsters on the 11th day of pregnancy were injected ip with 0.5 ml of dimethylsulfoxide containing 20, 50, 100, or 200 mg of AF-2 per kg body wt. To examine whether the hamster fibroblasts could produce 8-azaguanine (8AG)-resistant and 6-thioguanine (TG)-resistant mutants, those cells were treated directly with these chemicals and selected in minimal essential medium containing various concentrations of 8AG or 6TG. AF-2 and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were only moderately lethal to the cells, and the lowest percentage survival noted was 72.6%. The total numbers of mutants were counted in parallel plates, and the mutation frequency was calculated per 10^7 surviving cells. In control cultures selected with 8AG (10 $\mu\text{g}/\text{ml}$), there were 3.7 mutant colonies per 10^7 cells. No mutant colonies were observed with a dose of 8AG at 20 $\mu\text{g}/\text{ml}$ and selection medium containing 8AG at 30 $\mu\text{g}/\text{ml}$. However, AS-2 caused a 9.2- to 11.4-fold increase in the incidence of mutant colonies. MNNG caused a similar induction of mutant colonies to AF-2. AF-2 and MNNG produced a dose-dependent increase in 6TG-resistant mutants, and an approx 5- to 10-fold increase in mutant colonies was observed among

cells selected with medium containing 6TG. On transplacental application, doses of 100 mg and 200 mg of AF-2 per kg produced, respectively, almost 70-fold and over 150-fold increases in mutants selected with 8AG at 10 $\mu\text{g}/\text{ml}$. After treatment with AF-2 at 100 and 200 mg/kg, 4.3-13.5 mutant colonies were obtained. The results obtained on selection of these cells with 6TG were similar to those obtained on selection with 8AG. Ten colonies were cloned from mutants that received 100 mg of AF-2 per kg and were selected with 8AG at 20 $\mu\text{g}/\text{ml}$ and 6TG at 10 $\mu\text{g}/\text{ml}$. This work provides the first evidence that transplacental treatment with AF-2 causes gene mutations. (13 refs.)

- 77-0847 Metabolic Activation of 4-Nitroquinoline 1-Oxide and Its Binding to Nucleic Acid.** (Eng.) Tada, M.; Tada, M. In: *Fundamentals in Cancer Prevention. Proceedings of the 6th International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, 1975*. Magee, P. N.; Takayama, S.; Sugimura, T.; Matsushima, T., eds. (Baltimore: Univ. Park Press): pp. 217-228; 1976.

Recent findings are reported on the activation of 4-hydroxyaminoquinoline 1-oxide (4HAQO) by yeast seryl-tRNA (transfer RNA) synthetase and the binding of this reduced metabolite of 4-nitroquinoline 1-oxide (4NQO) to nucleic acid. 4HAQO is acylated by the seryl-AMP formed on the intermediary complex in the seryl-tRNA synthetase reaction, and seryl-4HAQO ultimately reacts with purine residues in the nucleic acid. Among the many aminoacyl-tRNA synthetases found in baker's yeast, only seryl-tRNA synthetase has the ability to activate 4HAQO. However, further examination of the amino acid dependency of 4HAQO-binding activity indicated that seryl- and prolyl-tRNA synthetases in *Escherichia coli* might participate in 4HAQO activation. The three kinds of adducts (two guanine and one adenine) formed when 4HAQO bound to poly(A) and poly(G) in vitro were identical to the major products found in RNA and DNA isolated from 4HAQO-treated cells could not be produced by the in vitro reaction of 4HAQO with synthetic homopolyribonucleotides. The adenine adduct was proposed to be either 3-(N⁶-adenyl)-4-aminoquinoline 1-oxide or 3-(N¹-adenyl)-4-aminoquinoline 1-oxide of 3-(N¹-adenyl)-4-aminoquinoline 1-oxide. (29 refs.)

- 77-0848 Development of Hemangiosarcomas in B6C3F₁ Mice Fed 2-Methyl-1-nitroanthraquinone.** (Eng.) Krishna Murthy, A. S. (Mason Res. Inst., Worcester, MA 01608) Baker, J. R.; Smith, E. R.; Wade, G. G. *Int J Cancer* 19(1): 117-121; 1977.

The incidence and histopathology of 2-methyl-1-nitroanthraquinone (MNA)-induced sc hemangiosarcomas (HS) in B6C3F₁ mice are described. One group of mice re-

received 0.06% MNA, the max tolerated dose (Group A), and one group received 0.03% MNA (Group B) mixed with standard chow for 548 days, followed by 120 days of stock diet. Most of the treated animals had to be sacrificed earlier because of moribund status. Wt differences were not significant for the 97 control and 172 treated mice. Survival included 13/47 male and 8/44 female mice in Group A and 19/44 males and 18/38 females in Group B, none of whom lived more than 338 days. In the control group, 77/80 mice survived the experimental interval of 671 days. HS developed in 88/90 male and 79/82 female mice; there were also 2 pulmonary adenomas and 14 lymphoreticular tumors. Tumor incidence did not vary significantly between Groups A and B. The sc HS were 0.2-3.0 cm and were usually located on the back or in the axilla; mesenteric HS occurred in six male and eight female mice. Pulmonary metastases were found in three males and one female. HS did not occur in the liver, spleen, or uterus, although 97% of Groups A and B mice developed tumors. The preferential localization in sc tissue surrounded by neutral fat is not explained. (16 refs.)

77-0849 **Investigation of Decomposition of Alkylating Mutagens of the Ethylenimine Series in Human Lymphocyte Culture.** (Eng.) Kirichenko, O. P. (Lab. Mutagenesis, Inst. Medical Genetics, Acad. Medical Sciences USSR, Moscow, USSR) Chebotarev, A. N.; Yakovenko, K. N. *Exp Biol Med* 81(5): 689-691; 1976.

The decomposition of alkylating mutagens of the ethylenimine series in human lymphocyte culture is assessed. To 1 ml of the sample, 0.4 ml methanol, 1 ml of a 5% soln of zinc sulfate, two drops of phenolphthalein soln, and the equivalent amount of a saturated soln of barium peroxide were added. The contents were mixed and centrifuged for 10 min at 6,000 rpm. The supernatant was then completely decanted, treated with 0.1 M acetate buffer (pH 4.6) and 0.2 ml of a 5% soln of 4-(p-nitrobenzyl)pyridine and acetone, mixed, and placed for 20 min in a boiling water bath. The tubes were then cooled on ice. To each tube were then added 0.6 ml acetone, 3.5 ml ethyl acetate, and 0.6 ml of 1 N sodium hydroxide. The contents were shaken and centrifuged for 1 min at 3,000 rpm. The top colored layer of ethyl acetate was drawn off into a cuvette and examined in a photoelectric colorimeter. Thiophosphamide was used in a final concentration of 10 µg/ml, whereas the final concentration was 30 µg/ml for dipin, fotrin, and phosphemid. In every case, the change in concentration of the alkylating substances with time could be described satisfactorily by a linear model. Thiophosphamide was not decomposed for 24 hr, either in the culture medium or in the lymphocyte culture. Fotrin, phosphemid, and dipin were appreciably decomposed in culture during the first 24 hr. However, no appreciable decomposition of these substances took place during the first 6 hr. Allowance must be made for the degree of decomposition of the mutagen utilized in the cell culture during the time that the substance is present in the culture. The method described can be used to determine

quickly and easily the degree of decomposition of alkylating compounds in cell cultures. (7 refs.)

77-0850 **Induction of Tyrosine Aminotransferase by Carcinogenic Metabolites of Tryptophan and Tyrosine.** (Eng.) Raushenbakh, M. O. (Oncological Scientific Center, Acad. Medical Sciences USSR, Moscow, USSR) Levchuk, A. A. *Bull Exp Biol Med* 82(9): 1330-1332; 1976.

Tyrosine aminotransferase (TA) was determined in rat liver 4 hr after ip injection of tryptophan metabolites or phenolic acids. TA activity was determined by a colorimetric method after 1 hr incubation; one extinction unit (EU) represented the formation of 1 µmole of p-hydroxyphenylpyruvate/g liver tissue. The av TA activity in livers from controls (saline injection only) was 71 EU; after 250 mg/kg anthranilic acid, 134; and after 250 mg/kg 3-hydroxyanthranilic acid, 218 EU. Phenyllactic acid did not cause an increase from the control value. (6 refs.)

77-0851 **Histogenesis of Urinary Bladder Cancer Induced in Rats by Bracken Fern.** (Eng.) Pamukcu, A. M. (Div. Clinical Oncology, Univ. Wisconsin Center Health Sciences, 1300 Univ. Ave., Madison, WI 53706) Erturk, E.; Yalciner, S.; Bryan, G. T. *Invest Urol* 14(3): 213-218; 1976.

The histogenesis of urinary bladder cancer induced in albino rats by bracken fern (*Pteris aquilinum*) is assessed. Twenty of 81 rats sacrificed between 2 and 11 wk on a bracken fern diet demonstrated only epithelial hyperplasias in varying degrees. Hyperplasia became apparent after 3 wk of feeding. During the next 4-6 wk, there was a progressive increase in epithelial hyperplasia, abnormal nuclei, and nuclear chromatin patterns. Between 8 and 10 wk, the hyperplastic epithelium demonstrated localized areas of nodular or papillary growth. Between 10 and 12 wk, a localized proliferative lesion was evident macroscopically. Fifty of 59 rats, surviving longer than 12 wk, developed epithelial tumors of the bladder. The nine rats with no tumors survived 17-30 wk after initiation of feeding. Epithelial tumors were either papilloma or carcinoma. Papillomas accounted for 7 of 50, and carcinomas accounted for 43 of 50 of the epithelial tumors. The first papilloma appeared in a rat after 12 wk of bracken fern feeding. Thereafter, six more rats developed papilloma at 15, 27, 28, 30, and 33 (two animals) wk. The first transitional cell carcinoma appeared in two rats after 12 wk of feeding. Undoubted invasion down to the level of the lamina propria was first seen at 12 wk. Thereafter, in the remaining 41 cases of carcinoma, infiltration extended into the lamina propria, superficial muscle, and deep muscle layers in 9, 12, and 20 cases, respectively. Metastases were observed in only 2 of 43 rats bearing bladder carcinomas. Squamous cell carcinomas were the most common (27 of 43). Transitional cell car-

cinoma was observed in 14 of 43 carcinomas. Only one case of adenocarcinoma was detected, and one carcinoma was a mixture of transitional and squamous cells. The majority of carcinomas (35 of 43) were papillary and had infiltrated the wall of the bladder. The results indicate that hyperplasia may precede bladder carcinoma in rats fed bracken fern. (33 refs.)

- 77-0852 Metabolic Consequences of Drug-induced Inhibition of the Pentose Phosphate Pathway in Neuroblastoma and Glioma Cells.** (Eng.) Kolbe, H. (Pharmakologisches Institut der Freien Universitat Berlin, Thielallee 69/73, D-1000 Berlin 33, W. Germany) Keller, K.; Lange, K.; Herken, H. *Biochem Biophys Res Commun* 73(2): 378-382; 1976.

Metabolic differences between rat C-1300 neuroblastoma cells (clone N2A) and C-6 glial cells after inhibition of the hexose phosphate pathway were investigated. During the stationary phase at a density of 1.5×10^5 cells/cm² for neuroblastoma cells and 4.5×10^5 cells/cm² for glial cells, the antimetabolite 6-aminonicotinamide (6-AN; 0.01 mg/ml) was added to the cultures. In both cell types, as in brain, 6-phosphogluconate (6-PG), which inhibits glucose phosphate isomerase, accumulated. Glioma cells contained three times more 6-PG than neuroblastoma cells. Intracellular gluconate, which can be released into the incubation medium, increases because of dephosphorylation of the accumulated 6-PG. Due to their higher dephosphorylating capacity, neuroblastoma cells had a gluconate content eight times their 6-PG content and four times the gluconate content observed in glioma cells. Glycolytic flux and ATP content of glioma cells were reduced, whereas no reduction was found in neuroblastoma cells. The glial cells appeared selectively vulnerable to 6-AN. (12 refs.)

- 77-0853 The Fate of [¹⁴C]Saccharin in Man, Rat and Rabbit and of 2-Sulphamoyl[¹⁴C]benzoic Acid in the Rat.** (Eng.) Ball, L. M. (Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England) Renwick, A. G.; Williams, R. T. *Xenobiotica* 7(4): 189-203; 1977.

The effect of prolonged exposure to dietary saccharin on the metabolism and excretion of ¹⁴C-saccharin was studied in rats, rabbits, and humans. ¹⁴C-Saccharin administered po was excreted entirely unchanged by rats and rabbits on a normal diet, by rats on a 1% and 5% saccharin diet for up to 12 mo, and by rabbits on a 1% saccharin diet for 6 mo. In the rat 90% of the dose was excreted in 24 hr, 70%-80% in the urine and 10%-20% in the feces. In the rabbit, 60%-80% of the dose was excreted in 24 hr, with 70% in urine and 3%-11% in feces. 3-¹⁴C-Saccharin taken po by three adult humans (1

woman, 2 men) was also excreted unchanged, 85%-92% in the urine in 24 hr both before and after taking 1 g of saccharin daily for 21 days. Saccharin was not metabolized in vitro by liver microsomal preparations nor by fecal homogenates from normal or saccharin-fed rats or by fecal homogenates from rats capable of converting cyclamate to cyclohexylamine. 2-Sulphamoyl-¹⁴C-benzoic acid given po to rats was excreted unchanged more slowly than saccharin. Saccharin clears less rapidly from the urinary bladder of both adult and fetal rats than from other tissues, suggesting that the bladder may be a target for any toxic action of saccharin. Whether this applies to man is not known. (30 refs.)

- 77-0854 Histological and Ultrastructural Changes in Rat Kidney Following Cadmium Injection.** (Eng.) Scott, R. (Dept. Urology, Royal Infirmary, Glasgow, England) Aughey, E.; Sinclair, J. *Urol Res* 5(1): 15-20; 1977.

The microscopic and ultrastructural effects of cadmium on glomeruli and tubular cells are described. Wistar rats were inoculated sc with 0.5 ml of cadmium chloride solution, which is equivalent to 0.17 mg cadmium/kg as a free ion. Repeat injections were made over a 6-mo period up to a maximum of five. The rats were sacrificed when they developed sc tumors or when they became ill. Light microscopy showed tubular degeneration and glomerular damage. Areas of desquamation and tubular cell damage were evident, and some tubules were filled with an amorphous material. The damage included hemorrhage, fibrosis, and cellular infiltration. These effects were most evident in the high-cadmium-dosage animals. The PAS reaction and the increased glomerular cellularity indicated an increase in the basement membrane. With the electron microscope, the podocytes in the glomerulus appeared as large cells with an extensive cytoplasm, a well-developed Golgi apparatus and associated smooth membranes, small areas of rough endoplasmic reticulum, and free ribosomes. Thickening of the basal lamina was observed in some areas. The nuclei of epithelial cells were commonly distorted, and intracellular dense fibrillar deposits were often present. Mesangial cells were observed singly or in groups, and they had many organelles. Dense ground substance was a characteristic of the mesangium in these glomeruli. Electron-dense deposits were found commonly in the greatly thickened parietal cell basement membrane. The membrane had a fibrillar appearance. Changes in the proximal convoluted tubule included electron-dense granular detritus filling the lumen, blebbing of microvilli, and a general increase in dense bodies. These changes were also observed in the distal convoluted tubule, but they were not as pronounced. (26 refs.)

- 77-0855 Putative Bronchial Chalones.** (Eng.) Houck, J. C. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 395-400; 1976.

dence is presented of a chalonelike substance from cow
 dog lung that is capable of inhibiting in vitro the growth
 a cell culture (A-427) originally derived from a human
 nchial carcinoma. The A-427 cells were cultivated in Dul-
 co's modified Eagle's MEM supplemented with 10%
 t-inactivated fetal calf serum, penicillin, streptomycin,
 glutamine. Under laboratory conditions the culture has
 doubling time of about 96 hr. Extracts, after ultrafiltration,
 the acetone powder of cow lung or from fresh dog lung
 to 64% and 60% inhibition, respectively, of the expected
 hr increment of growth. An ultrafiltrate prepared from the
 ed" medium from the cultivation of large numbers of A-
 cells in vitro led to even greater inhibition, but an ultrafil-
 e from fibroblasts with known fibroblast inhibitor activity
 without effect. The preliminary data suggest that there
 ht be a bronchial chalone that would be capable of affect-
 the mitotic control of human bronchial carcinoma cells
 vitro and, perhaps, in vivo. (6 refs.)

See also

* (Rev.): 77-0601, 77-0602, 77-0603, 77-0604, 77-0605,
 77-0606, 77-0607, 77-0608, 77-0609, 77-0610, 77-0611,
 77-0612, 77-0613, 77-0614, 77-0615, 77-0616, 77-0617,
 77-0618, 77-0619, 77-0620, 77-0621, 77-0622, 77-0623,
 77-0625, 77-0626, 77-0627, 77-0628, 77-0629, 77-0630,
 77-0631, 77-0632, 77-0633, 77-0634, 77-0635, 77-0636,
 77-0637, 77-0638, 77-0639, 77-0640, 77-0641, 77-0642,
 77-0643, 77-0644, 77-0645, 77-0646, 77-0647, 77-0648,
 77-0649, 77-0650, 77-0651, 77-0652, 77-0656, 77-0678,
 77-0684, 77-0717, 77-0720, 77-0730, 77-0744, 77-0761,
 77-0762, 77-0763, 77-0767.

* (Phys.): 77-0867.

* (Immun.): 77-1010, 77-1013, 77-1024, 77-1025,
 77-1027.

*(Path.): 77-1048, 77-1049, 77-1050, 77-1052, 77-1060,
 77-1119, 77-1130, 77-1131.

* (Epid.-Biom.): 77-1160, 77-1161, 77-1162, 77-1163,
 77-1164, 77-1167, 77-1168, 77-1169, 77-1170.

PHYSICAL CARCINOGENESIS

- 77-0856 Effect of Injury to the Microvessels on the Frequency of Tumor Cell Lodgment in Them.** (Eng.) Chernukh, A. M. (Lab. General Pathology and Experimental Therapy, Inst. General Pathology Pathological Physiology, Acad. Medical Sciences USSR, Moscow, USSR) *Bull Exp Biol Med* 82(7): 1069-1072; 1976.

The action of local laser injury to the microvessels on the frequency of tumor cell lodgment and on the ability of the cells to migrate from the lumen of the vessel was examined. After noninbred albino rats (200 g) were inoculated into the bloodstream with 0.1-0.3 ml of a tumor cell suspension (Zajdela's ascites hepatoma), the cells appeared in the mesenteric blood vessels. Of 84 hepatoma cells that passed along the vessels, only 9 cells finally lodged in them. Seven of these cells migrated with different degrees of activity. At the beginning, they changed their position relative to the vessel wall, but then they adhered to the wall and gradually migrated from its lumen. After laser injury to the vessel wall, the platelets moving along with the blood flow toward the site of injury settled above the injured area, and some of them remained there to form a juxtamural thrombus; others were carried away by the bloodstream. Of 65 hepatoma cells that entered the injured vessels, 53 lodged in the area of the microthrombus formation. A clot of platelets and a few WBC quickly formed around the lodged tumor cells. Of the 53 tumor cells that lodged, only 3 migrated outside the vessel. Injury to the wall of microvessels by laser radiation led to microthrombus formation and increased the lodging of tumor cells from 11% to 82%. (15 refs.)

- 77-0857 A Probable Radiation-Induced Epidermal Carcinoma in a Sheep.** (Eng.) West, J. L. (Veterinary Diagnostic Lab., Kansas State Univ., Manhattan, KS 66506) *Health Phys* 32: 32-34; 1977.

Epidermal carcinoma was discovered in 1 of 12 wether lambs given daily doses of ^{144}Ce - ^{144}Pr to investigate the effect of radionuclides on the alimentary tract. Just prior to feeding, individual doses (20 mCi in 1 ml soln) were placed in artificially created chambers in dehydrated alfalfa cubes. The sheep discussed in this report developed severe diarrhea on the 11th day of treatment and anorexia on the 16th day, at which time treatment was discontinued. The perineal and coccygeal regions were contaminated with radioactive ejecta. During the 16-day period, fecal collections monitored for radioactivity at a distance of 15 cm varied from 7,000-12,000 rads/hr. Ulceration and bacterial infection, which followed alopecia of the contaminated regions, responded to treatment with antibiotics. Healing occurred before biopsy specimens were taken from four areas in the contaminated regions (5.5 mo after treatment). Approx 4.5 yr after dosing, a firm enlargement was observed in the right ventrolateral coccygeal

region. As the enlargement increased in size, ulceration and bacterial infection occurred. The sheep was killed 59 mo after initial treatment, and a necropsy was done. A keratinized layer covered the thickened epidermis (5-15 cells) of the biopsy sections. Epidermal papillae were increased in thickness. In some sections, a few follicles and sebaceous and apocrine glands were seen, and an occasional adnexa was necrotic. Fibrous tissue had replaced areas of the dermal collagen. Foci of macrophages were in the dermis, and dilated apocrine glands with thickened hyalinized basement membranes were at the dermal-epidermal junction. The tumor was a firm, 3- x 7-cm grayish-white and red mottled mass. A sanguinopurulent exudate covered its ulcerated surface, and the sublumbar lymph nodes were enlarged. In ulcerated areas, the epidermis was absent or focally necrotic. Mitotic figures were frequent, and epithelial pearls were numerous. Groups of neoplastic cells were surrounded by a dense stroma of fibroblasts with delicate bipolar processes or a loose, myxomatouslike tissue. The arteriolar walls were thickened. Numerous foci of granulocytes and macrophages and several smooth muscle bundles were in the dermis. The findings are consistent with the diagnosis of locally invasive squamous cell carcinoma. (27 refs.)

- 77-0858 Breast Cancer Induced by Radiation: Relation to Mammography and Treatment of Acne.** (Eng.) Simon, N. (Dept. Radiotherapy, Mount Sinai School of Medicine, Fifth Ave. and 100th St., New York, NY) *JAMA* 237(8): 789-790; 1977.

The cases of 16 women with carcinoma of the breast who had been treated with radiation (75-1,000 rads) for acne or hirsutism 25-52 yr earlier are reported. Some of these patients had other sequelae associated with radiation treatment; four had skin cancer, two had benign and one had malignant thyroid nodules, and several showed atrophy, scarring, and telangiectasis of the facial skin. These observations indicate that radiation to the breast should be considered carcinogenic with no threshold dose. Mammography in young women should not be used for screening without further study of its effect. (12 refs.)

- 77-0859 Parathyroid Adenomas Induced by Radiation (Letter to Editor).** (Eng.) Albrechtsen, R. (Dept. Endocrine Surgery, Univ. Hosp., Rigshospitalet, DK-2100 Copenhagen, Denmark) Bruun, E.; Hasner, E.; Visfeldt, J. *Lancet* 1(8016): 854-855; 1977.

A case of parathyroid adenoma that developed following external irradiation is presented. The adenoma developed in a 66-yr-old euthyroid woman who had received radiation

therapy for a diffuse toxic goiter 30 yr earlier. Parathyroidectomy was performed, and histologic examination showed that the adenoma consisted of dilated and tortuous tubules lined with irregular epithelium. Irregular positions of the nuclei, nuclear polymorphism, and several giant nuclei with large nucleoli were seen in the tumor cells. The histologic features of this adenoma differed from all other hyperparathyroid adenomas examined over a 35-yr period. When a parathyroid adenoma of unusual histopathological pattern is found, radiation-induced tumor should be considered. (no refs.)

77-0860 Studies into the Transplantation Biology of Ultraviolet Light-induced Tumors. (Eng.) Daynes, L. A. (Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, UT 84132) Spellman, C. W.; Woodward, J. G.; Stewart, D. A. *Transplantation* 23(4): 343-348; 1977.

Fluorescent UV irradiation rendered syngeneic mice susceptible to tumors that would normally have been rejected. The susceptibility was achieved after 2 wk of five 30-min exposures/wk. The immunoregulatory effect of UV exposure appeared to be additive, because a direct correlation existed between the rate of tumor growth and the length of UV exposure prior to tumor implantation. It was also possible to cause tumor susceptibility by confining the site of irradiation to the tail. The mice remained resistant to subsequent tumor implantation if the UV-irradiated tails were amputated immediately following UV exposure. This suggests that the mechanism underlying UV-induced tumor susceptibility is not directly mediated by UV light but results from secondary manifestations initially triggered by the UV exposure. UV-irradiated mice could also be immunized against UV tumors, suggesting that immune recognition of tumor-specific transplantation antigens was not inhibited. The development of tumors after chronic UV exposure appears to be the product of both the carcinogenic properties of UV light as well as its ability to alter normal immunological reactivity. (8 refs.)

77-0861 Low-Level DNA Exchanges in Normal Human and Xeroderma Pigmentosum Cells after UV Irradiation. (Eng.) Fujiwara, Y. (Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-12, Ikuta-ku, Kobe 650, Japan) Tatsumi, M. *Mutat Res* 43(2): 279-290; 1977.

Evidence for the existence of recombinant DNA exchanges in normal human skin fibroblasts and two types of Xeroderma pigmentosum (XP) cells (XP3KO, XP4KO) following UV irradiation was obtained. Cells were irradiated with UV (10 joules/meter²); both irradiated and unirradiated cells were labeled and examined for the transfer of sensitive sites from parental to daughter DNA strands using the T4 endonuclease V assay method. Analysis of sedimentation rates revealed that DNA from irradiated cells treated by the en-

zyme sedimented much more slowly than those not treated or normal cells treated by the enzyme. The enzyme thus specifically nicked the double-stranded DNA with the dimers. Loss of detected sensitive sites from 24-hr-incubated XP and normal cells was about 80%. There was no difference between cells tested immediately after irradiation and those tested after 4 hr. This dimer loss was ascribed solely to DNA exchanges. An attempt to show post UV DNA exchange by CsCl isopycnic centrifugation was unsuccessful. The transfer of sensitive sites observed 24 hr after 10 joules/m² was lower in normal cells than in excision-defective XP cells, since the dimers were removed effectively by the normal excision repair before and after exchanges during the post-UV incubation period. (18 refs.)

77-0862 DNA Repair and Malignancy (Meeting Abstract). (Eng.) Ringborg, U. (Radiumhemmet, Karolinska Sjukhuset, Stockholm, Sweden) *Hereditas* 84: 131; 1976. (no refs.)

77-0863 The Inhibition of Repair in UV Irradiated Human Cells. (Eng.) Collins, A. R. (Dept. Zoology, Univ. Cambridge, Cambridge, CB2 3EJ, England) Schlör, S. L.; Johnson, R. T. *Mutat Res* 42(3): 413-432; 1977.

The effects of hydroxyurea (HU) on excision repair in UV-irradiated HeLa cells were determined with the use of three different assays. At the cytological level, incubation of UV-irradiated metaphase cells with HU caused chromosome decondensation. A modified alkaline-sucrose gradient sedimentation technique revealed a marked retardation in the sedimentation of DNA from UV-irradiated cells incubated for a short period with HU. The effect of HU on the incorporation of (³H)thymidine by UV-irradiated G1 cells depended upon the concentration of thymidine in the medium. Chromosome decondensation and retarded DNA sedimentation occurred also after incubation of irradiated HeLa Cells with deoxyadenosine (DX) but not thymidine, at concentrations which inhibit semiconservative DNA synthesis. The effects of HU or DX on chromosomes and DNA were not seen if all four deoxyribonucleoside precursors of DNA were supplied exogenously. The results point to an inhibition of repair DNA synthesis by HU or DX, at the level of the supply of DNA precursors. These agents inhibit semiconservative DNA synthesis in a similar manner. In the presence of these inhibitors, single-strand gaps accumulate in the DNA. (54 refs.)

77-0864 Semi-conservative Deoxyribonucleic Acid Synthesis in Unirradiated and Ultraviolet-Irradiated Xeroderma Pigmentosum and Normal Human Skin Fibroblasts. (Eng.) Rude, J. M. (Lab. Experimental On-

cology, Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA 94305) Friedberg, E. C. *Mutat Res* 42(3): 433-442; 1977.

Rates of semiconservative DNA synthesis were investigated in asynchronous xeroderma pigmentosum (XP), an XP variant line, and normal human skin fibroblasts using cellular autoradiography. In the unirradiated cells, no differences in DNA synthesis were detected. UV irradiation led to a decreased rate of DNA synthesis for at least 3 hr in all three cell strains. In the normal cell strain, recovery of the rate of DNA synthesis occurred at later times following a UV fluence of 5 J/meter². At this UV fluence no recovery occurred in classical XP cells during a 24-hr post-irradiation period; it was slower than normal in the XP variant. These results, considered in terms of current models of DNA replication in UV-irradiated cells, indicate: (1) that pyrimidine dimers are very effective blocks to DNA synthesis and (2) that there is no inherent defect in semiconservative DNA synthesis in either classical XP or XP variant cells which is independent of a defect in DNA repair capacity. This suggests that the restitution of DNA synthetic capacity after UV irradiation is critically dependent on a cells' capacity to excise thymine dimers. (23 refs.)

- 77-0865 **Defective Repair of Ultraviolet- and Gamma-Ray Damaged DNA in Fanconi's Anaemia.** (Eng.) Rainbow, A. J. (Dept. Radiology, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada) Howes, M. *Int J Radiat Biol* 31(2): 191-195; 1977.

An alteration in DNA repair in fibroblasts from a Fanconi anemia (FA) patient after infection with irradiated suspensions of adenovirus type 2 (Ad 2) is reported. The DNA repair was compared to that of normal human fibroblasts. The ability of Ad 2 to form viral structural antigens (VA g) in the fibroblasts was assayed by immunofluorescent staining 48 hr after infection of monolayers. The frequency of viral structural antigen (VA g)-positive cells was similar for both the FA and normal lines when infected with unirradiated virus. However, after UV irradiation (10³ J/meter²) of Ad 2, the frequency of VA g was markedly lower in the FA fibroblasts than in the normal fibroblasts. This study and another using large doses of gamma irradiation indicate a defective DNA repair mechanism in the FA cell line. Since previous work indicates there is no deficiency in 5,6-dihydroxydihydrothymine (*t*) excision in the FA line, it may be defective in the repair of some other gamma-ray-induced lesion. (14 refs.)

- 77-0866 **Effects of β -Carotene on Ultraviolet Induced Cancer Formation in the Hairless Mouse Skin.** (Eng.) Epstein, J. H. (Univ. California Medical Sch., San

Francisco, CA 94143) *Photochem Photobiol* 25(2): 211-213; 1977.

In a study on hairless mice exposed to UV irradiation, tumors appeared earlier and grew more rapidly in placebo-treated animals than in those treated with β -carotene (CR). Beadlets containing 10% of β -carotene were dissolved in water at 1 g/4 ml, and the doses used were 0.4 ml ip 3 \times /wk for 1 mo, then 0.2 ml ip 3 \times /wk for 5 mo. Injections were discontinued in the 61 CR and 56 placebo mice after 6 mo because of the high mortality in both groups. The placebo injection was prepared from beadlets without CR. One month after starting the injections, the UV (6.5 \times 10³ J/meter²) irradiation was started and continued 3 \times /wk for 15 mo. Among survivors at the end of 15 mo, tumors > 4 mm² and 50 mm² were seen in 10/11 and 9/11 CR mice, respectively, compared to 20/21 and 20/21 placebo mice, respectively. Autopsies of five CR and three placebo mice revealed well-differentiated squamous cell carcinomas which had invaded into the dermis and subcutaneous tissue. (11 refs.)

- 77-0867 **The Effects of U.V.-Light, Ionizing Radiation and the Carcinogen N-Acetoxy-2-fluorenylacetamide on the Development In Vitro of One- and Two-Cell Mouse Embryos.** (Eng.) Ku, K. Y. (Natl. Inst. Environmental Health Sciences, Natl. Inst. Health, P. O. Box 12233, Research Triangle Park, NC 27709) *Int J Radiat Biol* 30(5): 401-408; 1976.

The influence of UV light, ionizing radiation, and N-acetoxy-2-fluorenylacetamide (NAFAA) on the development in vitro of one- and two-cell embryos of DC₁ and C₃H₂F₁/J mice is studied. Embryos exposed 18 hr after human chorionic gonadotropin (HCG) administration were very sensitive to UV radiation. Following a dose of 0.5 Joule/meter², only 50% of the embryos reached or passed first cleavage by day 2 compared with 97% in untreated cells. Most of the treated embryos were arrested at the two-cell stage, and when incubated underwent gradual deterioration. One-cell embryos obtained 24 hr after HCG injections developed better than the more immature embryos but also demonstrated arrested development at the one-cell stage after being exposed to UV radiation. However, by day 4, 12% of the embryos did reach the four-cell level after treatment with 0.5 Joule/m². Attempts to reverse the UV-radiation cleavage by exposing the eggs immediately after treatment to light at 365 nanometers were unsuccessful. Embryos that underwent first cleavage in vivo developed better than one-cell embryos and were more resistant to UV-radiation. Two-cell embryos matured to blastocysts almost as well as the unexposed cells. However, at a higher dose (10 Joules/m²), development was hindered. After 2 days of incubation, only 59% of the embryos reached the morula stage. Thereafter, these cells degenerated quickly, and only 10% became blastulas at day 4. When radiation was delivered at 2 Joules/m²/sec, development of the eggs stopped after the second cleavage. When embryos were ex-

posed to x-rays (100 rads) 24 hr after HCG injections, only 10% of the embryos developed past the four-cell stage. At a high dose (500 rads, 38 rads/min), only 10% of the embryos matured to blastocytes 4 days after exposure. At this time, 7% of the embryos had degenerated. Embryos treated 18 hr after HCG injections were sensitive to 0.7 μ M NAFAA. None developed beyond the two-cell stage. When older embryos (24 hr after HCG) were treated with the carcinogen, 3% of the cells matured to morula-blastula stages compared with 45% of controls. The presence of the chemical appeared to arrest the embryos at the one- and two-cell stages. At 7 μ M NAFAA, the maturation process was suppressed. After 3 days of incubation, only 27% of the cells were at the morula stage. By day 4, only 14% were at the blastula level. Mouse embryos at the one-cell stage are more sensitive than those at the two-cell stage. (14 refs.)

77-0868 **Interaction of Hyperthermia with Radiations of Different Linear Energy Transfer.** (Eng.) Gerner, E. W. (Dept. Radiology, Div. Radiation Oncology, Univ. Arizona Health Sciences Center, Tucson, AZ 85724) Leith, J. T. *Int J Radiat Biol* 31(3): 283-288; 1977.

Single-cell survival parameters were measured after the cells were heated (in constant-temperature water baths) and then immediately exposed to different linear energy transfer (LET) radiations to study how hyperthermia interacts with radiation as a function of LET. Chinese hamster ovary (CHO) cells were exposed to 37 or 43 C for 1 hr and then irradiated with either 4-million-electron-volt x-rays or accelerated carbon ions in the peak region of the ionization curve. Hyperthermia interacted synergistically with the low-LET x-rays, but the interaction was essentially additive with the high-LET accelerated carbon ion radiation. (8 refs.)

77-0869 **Exposure to Sunlight and Urinary Excretion of 5-S-Cysteinyldopa.** (Eng.) Rorsman, H. (Dept. Dermatology, Univ. Lund, Lund, Sweden) Agrup, G.; Falck, B.; Rosengren, A. M.; Rosengren, E. *Pigm Cell* 2: 284-289; 1976.

The urinary excretion of 5-S-cysteinyldopa, an amino acid whose concentration in the urine is a sensitive method for the chemical diagnosis of metastasizing melanomas, was determined in 14 healthy individuals to determine normal seasonal variations. The mean 24-hr excretion level in autumn was 84 μ g, in winter 60 μ g, in spring 94 μ g, and in summer 191 μ g. The scatter of values was lowest in winter, intermediate in autumn and spring, and highest in summer. The highest summer values were 384 and 378 μ g/24 hr and the lowest, 93 μ g. These variations are related to exposure to sunlight, and they illustrate how sensitively the excretion of 5-S-cysteinyldopa reflects what is happening in the melanocytes. Previous exposure to sunlight must be considered in the assessment of urinary 5-S-cysteinyldopa when following up patients treated for melanoma. (12 refs.)

See also

- * (Rev.): 77-0607, 77-0618, 77-0678, 77-0684, 77-0708, 77-0715, 77-0716, 77-0717, 77-0718, 77-0719, 77-0720, 77-0724, 77-0730, 77-0767.
- * (Chem.): 77-0772, 77-0784, 77-0820.
- * (Viral): 77-0890, 77-0916, 77-0954.
- * (Immun.): 77-1008, 77-1027.
- * (Path.): 77-1079, 77-1080, 77-1087, 77-1090, 77-1119.
- * (Epid.-Biom.): 77-1159, 77-1165, 77-1166.

VIRAL CARCINOGENESIS

77-0870 The Initiation Sites of Rous Sarcoma Virus RNA-Directed DNA Synthesis in Vitro. (Eng.)

Cashion, L. M.; Joho, R. H.; Planitz, M. A.; Billeter, M. A.; Weissmann, C. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 147-159; 1976.

The origin and complexity of the DNA synthesized by disrupted Rous sarcoma virus, Prague B strain (Pr RSV-B), were examined. The DNA was annealed with Pr RSV-B ³²P-RNA, and the hybridized RNA was isolated and characterized by digestion with RNase T₁ and identification of the resulting large oligonucleotides. The location on the viral RNA of regions complementary to cDNA was determined from the map of large T₁ oligonucleotides of Pr RSV-B RNA. The most frequent DNA species corresponded to a region of about 200 nucleotides from the 5' terminus. DNA complementary to several other regions of the viral RNA, particularly one located toward the middle of the molecular, was also present in varying, lower amounts. These findings suggest that the major initiation site is located near the 5' terminus, but that DNA synthesis may also start at various other positions throughout the genome. (24 refs.)

77-0871 Defectiveness in the Bryan High Titer Strain of Rous Sarcoma Virus. (Eng.)

Murphy, H. M. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 243-256; 1976.

The transformation of quail and turkey fibroblasts by the Bryan high-titer Rous sarcoma virus and analysis of the defective particles produced, are described. High titers of cloned helper-independent defective particles were produced to study defective RNA tumor virus genomes. Two new replication-defective viruses were generated that are similar to the known variants BH-RSV(-), and BH-RSV α (RAV-49). The envelope-defective BH-RSV(-) virus was elaborated by 16Q transformed quail cells. Transformed turkey cells strain α 40T produced large quantities of noninfectious BH-RSV α particles. Another new replication-defective variant was produced by transformed turkey cell strain α 48T. Biological rescue and complementation studies showed that this virus lacks a functional reverse transcriptase, although it carries a determinant for subgroup A envelope glycoprotein. A diagram of the derivation of the transformed cell strains (16Q, α 40T, and α 48T) is included. (23 refs.)

77-0872 Body Temperature and Tumor Virus Infection. I. Tumorigenicity of Rous Sarcoma Virus for Reptiles. (Eng.)

Trubcheninova, L. P. (Cancer Res. Center, Acad. Medical Sciences USSR, 115 478 Moscow, USSR) Khutoryansky, A. A.; Svet-Moldavsky, G. J.; Kuznetsova, L. E.; Sokolov, P. P.; Belianchikova, N. I. *Neoplasma* 24(1): 3-19; 1977.

The tumorigenicity of Rous sarcoma virus (RSV) was studied in 22 reptile species representing 10 families of the orders Chelonia and Squamata. RSV did not induce tumors in 13 inoculated species. In nine species, RSV induced polymorphous sarcomas with spindle-shaped (fibroblastlike), round, and polygonal macrophagelike cells and, occasionally, giant polynuclear cells. Chromosome analysis indicated that the tumors originated in the reptile cells. Tumors were induced in adult reptiles with a latent period of only 1-3 mo by inoculation with a 30% cell-free homogenate of Schmidt-Ruppin strain RSV (4×10^7 sarcomagenic doses per snake; 10^6 - 10^7 sarcomagenic doses per lizard). The case of tumor induction suggests that reptiles are more susceptible to this strain of RSV than mice, rats, guinea pigs, rabbits, and monkeys. The tumors of two snakes were tumorigenic in chickens. Since RSV is oncogenic for a wide range of birds and mammals as well as reptiles and since these three classes belong to the same group, the pathogenicity of RSV for these animals appears to be predetermined by evolution. Elevation of body temperature within certain limits probably transforms a symptomless viral infection into a viral disease. (57 refs.)

77-0873 Oncogenic Transformation of Chick-Embryo Fibroblasts by Rous Sarcoma Virus Alters Rubidium Uptake and Ouabain Binding. (Eng.)

Banerjee, S. R. (Dept. Pharmacology, M. Herbert Eisenhart Tissue Culture Lab., Univ. Rochester, Sch. Medicine and Dentistry Rochester, NY 14642) Bosmann, H. B.; Morgan, H. R. *Exp Cell Res* 104(1): 111-117; 1977.

The influence of oncogenic transformation of chick embryo fibroblasts (CEF) by Rous sarcoma virus (Schmidt-Ruppin strain) on ouabain binding and rubidium uptake was evaluated. The specific binding of H³-ouabain was significantly higher to untransformed CEF than to 3T3 cells on a per cell or per mg of protein basis. Ouabain binding to the transformed CEF, however, was markedly decreased. The binding was 2.5 times higher in untransformed CEF than in transformed CEF. There was a reciprocal relationship between the degree of cell transformation and the quantity of ³H-ouabain bound at the CEF surface. The ouabain-sensitive Rb86 uptake in

untransformed cells remained linear for at least 45 min, whereas in transformed cells the uptake remained linear for only 30 min. This uptake was significantly less in transformed cells compared to untransformed cells. The initial velocity of the uptake in transformed cells was reciprocal to the degree of cell transformation. A comparison of parameters in CEF at 37 C and temperature-sensitive virus (ts-68)-transformed cells at 37 C showed a more pronounced decrease in the ouabain-sensitive Rb86 uptake and specific H3-ouabain binding in the virally transformed CEF compared to that of untransformed cells. The results suggest that alterations in cation transport may be intimately related to oncogenic cell transformation. (28 refs.)

77-0874 Regulation of Sugar Transport in Chick Embryo Fibroblasts and in Fibroblasts Transformed by a Temperature-Sensitive Mutant of the Rous Sarcoma Virus. (Eng.) Kletzien, R. F. (Sidney Farber Cancer Center, 44 Binney St., Boston, MA 02115) *J Cell Physiol* 89(4): 723-728; 1976.

The regulation of sugar transport in transformed (by a temperature-sensitive mutant of Rous sarcoma virus) and normal chick embryo fibroblasts (CEF) was assessed. The addition of fetal calf serum to serum-deficient CEF resulted in a biphasic increase in the sugar transport rate. The first increase in transport occurred within 10 min of serum addition, and it was not blocked by prior addition of actinomycin D or cycloheximide. The transport started to increase again 45-60 min after serum addition. The second increase was blocked by cycloheximide but not by actinomycin D. Cordycepin (10 µg/ml) blocked the second phase of the increase in sugar transport as effectively as did cycloheximide. The effects of actinomycin D, cordycepin, and cycloheximide on the transport increase induced by hexose starvation were determined. In contrast to the increases induced by serum stimulation of CEF, actinomycin as well as cordycepin and cycloheximide were effective in blocking this transport increase. The data indicate the rapidity with which transport activity changed when Ts68-infected CEF were shifted from the nonpermissive (41 C) to the permissive (37 C) temperature for transformation or vice versa. The greatest rate of change occurred in the first 6 hr after a temperature shift. Actinomycin D did not block the increase in transport when cultures were shifted from 41 to 37 C, but cycloheximide did. Ts68-infected CEF cultured at 41 C responded to serum removal and addition, as did uninfected CEF. However, Ts68-infected CEF cultured at 37 C did not exhibit changes in the max velocity for transport in response to serum addition or removal. These cultures continuously expressed an elevated transport rate. When Ts68-infected CEF were incubated in glucose-free medium at 37 or 41 C, the max velocity differences for sugar transport disappeared between the transformed and untransformed cells. The key to understanding transformation may lie in understanding the means by which the temperature-sensitive viral gene product alters regulation. (17 refs.)

77-0875 Studies on the Synthesis and Structure of Mitochondrial DNA in Cells Infected by Rous Sarcoma Viruses and on the Occurrence of Intramitochondrial Virus-like Particles in Certain RSV-induced Tumor Cells. (Eng.) Nass, M. M. (Dept. Therapeutic Res., Univ. Pennsylvania, Sch. Medicine, Philadelphia, PA 19174) *Mol Cell Biochem* 14(1-3): 121-128; 1977.

Distinct changes in mitochondrial DNA (mtDNA) upon oncogenic virus-induced transformation are described. Primary chick embryo fibroblasts (CEF) were prepared from 10-day-old chick embryos and infected with either the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) or a temperature-sensitive mutant (T5). All cells were grown at 36 C for 5 days, and then half of the cultures were placed at 41 C and half at 36 C. The incorporation of tritiated thymidine was used to measure the synthesis of mtDNA in vivo after the injection of wild-type RSV. mtDNA synthesis increased from two to four times in infected cells. Stimulation of mtDNA synthesis in transformed cells was temperature-dependent when T5 mutants were used to infect the cells. Replicative intermediates of mtDNA molecules in uninfected and in transformed CEF showed that mtDNA replicates by displacement synthesis. Monomeric and catenated dimeric mtDNA molecules of the D loop and expanded D loop forms were observed. Band sedimentation and electron microscopic methods revealed that mtDNA samples contained from 200 to 1,500 nucleotides. Heteroduplex formation by restriction fragments of mtDNA revealed a small region of apparent nonhomology in 2% of the CEF/CEF-SR heteroduplex molecules, in 1% of the CEF-SR/CEF-SR homoduplex molecules, and in none of the CEF/CEF homoduplex molecules. Intramitochondrial viruslike particles (IMV) were observed in RSV-induced hamster tumor cells, whether or not they were fused with other types of cells. Treatment of RSV-induced hamster tumor cells with bromodeoxyuridine enhanced the frequency of IMV, with more mitochondria exhibiting IMV and more IMV per mitochondrion. (30 refs.)

77-0876 Specific Changes in the Synthesis of Mitochondrial DNA in Chick Embryo Fibroblasts Transformed by Rous Sarcoma Viruses. (Eng.) D'Amato, M. A. (Dept. Therapeutic Res., Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19174) *J Cell Biol* 71(3): 781-794; 1976.

Alterations in the synthesis of mitochondrial DNA in chick embryo fibroblasts transformed by Rous sarcoma viruses are studied. The three-to-fivefold increase in the specific activity of mtDNA from transformed cells (WT36, WT41, T536) was not the consequence of a comparable increase in the mass of mitochondria in the transformed cells or the concentration of covalently closed circular mitochondrial DNA in these cells. The rate of mitochondrial DNA synthesis in vitro was fivefold greater in mitochondria isolated from cells transformed with the wild type virus (WT36, WT41) than in non-transformed, uninfected cells (C36, C41). In mitochondria isolated from normal cells (C36, C41) or T5-infected cells

with nontransformed phenotypes (T541), mt DNA synthesis in vitro was significantly inhibited by mercaptoethanol. In contrast, the in vitro DNA synthesis by mitochondria isolated from morphologically transformed cells (WT36, WT41, T536) was only slightly inhibited by mercaptoethanol. DNA polymerase activity was sevenfold greater in mitochondrial extracts prepared from cells transformed with the wild type virus (WT36, WT41) than in nontransformed, uninfected cells (C36, C41). In mitochondrial extracts prepared from cells infected with the temperature-sensitive virus (T536, T541), the increase in DNA polymerase activity occurred only at the permissive temperature (T536). At the nonpermissive temperature (T541), the DNA polymerase activity was characteristic of that in mitochondrial extracts prepared from uninfected cells. Further investigation is needed to show whether mitochondrial DNA synthesis is an essential factor in the transformation response of the host cell to the oncogenic virus infection or whether the observed mitochondrial effects are of a more peripheral nature. (26 refs.)

- 77-0877 **Temperature-Sensitive Mutants of Avian Sarcoma Viruses: Genetic Recombination Between Multiple or Coordinate Mutants and Avian Leukosis Viruses.** (Eng.) Blair, D. G. (Cancer Res. Lab., Univ. Western Ontario, London, Ontario, Canada, N6A 2K6) Masson, W. S.; Hunter, E.; Vogt, P. K. *Virology* 75(1): 48-59; 1976.

Five coordinate (class C) temperature-sensitive (*ts*) mutants of avian sarcoma viruses that fail to transform or replicate at 41°C were analyzed by genetic recombination. C/E chf-chick embryo fibroblasts were infected with avian leukosis RAV-6 and appropriate dilutions of a *ts* mutant. For LA337 and LA338 mutants, from 9-13% of the transforming activity present in the mixed harvest had recombined with RAV-6 for the host range marker. Properties of subgroup B sarcoma virus progeny indicated that all recombinant clones were able to replicate at 41°C, but remained *ts* for focus formation. Thus, the mutants LA334, LA338, LA336 and LA343 apparently carry multiple mutations which can be grouped into two categories; all four seemed to carry a *ts* lesion in the transformation (T) function. Chick embryo fibroblasts preinfected with RAV-6 clearly complemented the *ts* replication (R) functions in LA334, LA338 and LA343. Serial cloning data suggest that LA336 carries both an early transient and a late continuous mutation affecting transformation; an early class C mutation is in accord with the fact that LA336 has a thermolabile virion DNA polymerase. Because the class R or class C *ts* markers in LA334, LA336, LA337 and LA338 show a rate of high segregation from *env* (coding for envelope glycoproteins), their *ts* lesions are probably located outside the *env* region. In LA343 the rate of segregation between *env* and the class C or R *ts* lesion is less than in the other mutants, indicating that LA343 could have a lesion in *env*. A high frequency of recombination was even observed upon analysis of subgroup C sarcoma virus progeny selected for the parental *src* (sarcomatous transformation) and *env* markers. (27 refs.)

- 77-0878 **Solubilization of Initial Attachment Site Activity for Avian Tumor Viruses with Lithium Diiodosalicylate.** (Eng.) Moldow, C. F. (Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN 55455) McGrath, M.; Peterson, C. *Proc Soc Exp Biol Med* 154(2): 201-205; 1977.

The solubilization of a cell surface attachment site for avian tumor viruses (ATV) from chicken embryo fibroblast (CEF) plasma membranes with lithium 3,5-diiodosalicylate (LIS) was investigated. An LIS extract of CEF plasma membranes was examined to determine whether this extract would interact with virus in vitro to impair subsequent virus binding by CEF plasma membranes. Bryan strain Rous sarcoma virus and Rous-associated viruses RAV-1 and RAV-2 were used to prepare the pseudotypes RSV(RAV-1) and RSV(RAV-2). RSV(RAV-1) was incubated either with CEF LIS extract or buffer and then exposed to CEF membranes to assay viral attachment. Attachment was consistently reduced by the CEF LIS extract. There was a 55% reduction in RSV(RAV-1) binding after incubation with 19 µg of CEF LIS extract. Attachment of RSV(RAV-2) was inhibited to a similar degree by the LIS extract. LIS extracts of plasma membranes obtained from between 2 and 6 x 10⁷ CEF's retarded the binding of 5 x 10⁵ focus-forming units of RSV(RAV-1) by approx 50%. The individual extracts had equal amounts of protein and neutral sugar, and membranes from 3 x 10⁶ CEF's yielded 1 µg (neutral sugar) of LIS extract. The inhibitory activity remained with the supernatant fluid after centrifugation for 30 min and was recovered in the aqueous phase after chloroform-methanol (3:1) extraction. Preincubation of RSV(RAV-1) with LIS extract also reduced virus infectivity. Glycophorin prepared by LIS extraction of human RBC ghosts was compared to a CEF LIS extract to determine the relative capacity of each to inhibit ATV attachment to CEF membranes. Glycophorin did not antagonize RSV(RAV-1) attachment as well as LIS extracts of CEF. Membranes from approx 200 RBC had to be extracted to produce the activity of a single CEF. The extraction of CEF plasma membranes with LIS solubilizes membrane components that interact directly with ATV in vitro, antagonizing ATV binding to CEF plasma membranes and reducing the transforming capacity of these viruses. (12 refs.)

- 77-0879 **A New, not Virus Related Reverse Transcriptase in the Chicken System.** (Eng.) Bauer, G.; Jilek, G.; Hofschneider, P. H. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects.* Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): pp. 515-530; 1976.

The isolation and partial characterization of a reverse transcriptase from particles in the allantoic fluid of 10-day-old embryonated SPF-VALO chicken eggs is described. The enzyme was shown to be a true reverse transcriptase by its template characteristics and its ability to synthesize a faithful

transcript of heteropolymeric RNA. In order to determine whether the particle enzyme was related to or identical with reverse transcriptase from chicken viruses, its sedimentation constant was compared with those of reverse transcriptases of reticuloendotheliosis virus (REV) and AMV. Although the particle enzyme sedimented at the same rate as AMV enzyme, it was clearly distinguished from REV enzyme both in terms of its sedimentation constant and its preference for different divalent cations. Since antibody against AMV reverse transcriptase has been shown to inhibit the activity of all viruses of the avian leukosis viruses/avian sarcoma viruses (ALV/ASV) group, the inhibition of particle and AMV enzyme by immunoglobulin G against AMV reverse transcriptase was studied in parallel immunoglobulin G dilution assays. Whereas AMV enzyme was inhibited very efficiently by small amounts of immunoglobulin G, there was only a weak effect on the reverse transcriptase purified from the particles. Thus, the particle enzyme appeared to be only weakly, if at all, related to the reverse transcriptase of the viruses from the ALV/ASV group. Since the particle enzyme could not be related to the above two chicken viruses (the only ones known to contain reverse transcriptase), the enzyme appears to be a good candidate for a cellular reverse transcriptase. (16 refs.)

77-0880 Differences in the Glycoproteins of Avian Tumor Virus Recombinants: Evidence for Intragenic Crossing Over. (Eng.) Galehouse, D. M.; Duesberg, P. H. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. J., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 227-236; 1976.

Recombination among avian RNA tumor viruses has been shown to occur by crossing over at different sites of the parental envelope genes to generate different recombinant glycoproteins. The recombinants inherit their sarcoma gene from a sarcoma virus and their host range marker from a leukosis virus. With avian tumor viruses, the host range is determined by a major viral envelope glycoprotein, gp85. Differences among the gp85's of the recombinant viruses were investigated. The viruses were labeled with ^3H - or ^{14}C -glucosamine, and the glycopeptides were prepared by pronase digestion. The recombinant and parental virus glycoproteins were analyzed by polyacrylamide electrophoresis. The glycoproteins of five recombinants selected for the sarcoma gene of Prague Rous sarcoma virus of subgroup B and the envelope glycoprotein of RAV-3 leukosis virus of subgroup A were compared to those of their parents. The electrophoretic mobilities differed among the different recombinant viruses, although all the glycopeptides were of the same size. The carbonate to protein ratios of the glycoproteins were estimated from their buoyancy densities in cesium chloride gradients. These ratios correlated to differences in electrophoretic mobility. It is concluded that the glycoproteins of different recombinants differ in the number of carbohydrate chains they contain and, hence, presumably reflect different intragenic crosses. (11 refs.)

77-0881 Detection and Enumeration of Transformation-Defective Strains of Avian Sarcoma Virus with Molecular Hybridization. (Eng.) Stehelin, D. (Dept. Microbiology, Univ. California, San Francisco, CA 94143) Fujita, D. J.; Padgett, T.; Varmus, H. E.; Bishop, J. M. *Virology* 76(2): 676-684; 1977.

Propagation of avian sarcoma viruses (ASV) leads to the formation of genetic variants that cannot induce sarcomas or transform fibroblasts in culture. Such transformation-defective (td) strains are deletion mutants that lack 10%-20% of the genetic information of the parent virus. To study these td strains, single-stranded DNA (cDNA-sarc) complementary to the nucleotide sequences deleted from the genome of ASV during the genesis of td variants was prepared. cDNA-sarc can hybridize to genome RNA from any strain of ASV, but it cannot react with RNA from td variants, and this specificity was incorporated in an assay for td virus, that permits the rapid and accurate enumeration of td deletions. The process can also be applied to deletions in other viral genes. All 20 copies of the proviral DNA for ASV in XC cells were shown to contain *src* (the viral gene for the maintenance of cellular transformation by ASV). It was also shown that single avian cells can contain functioning proviruses for both ASV and a congenic deletion mutant. Available evidence suggests that the deletion of *src* arises during the synthesis or integration of proviral DNA, not during transcription of viral RNA from provirus. (21 refs.)

77-0882 Glycolipids of Chick Embryo Fibroblasts Infected with Temperature-sensitive Mutants of Avian Sarcoma Viruses. (Eng.) Hakomori, S. (Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, and Depts. Pathobiology and Microbiology, Univ. Washington, 1124 Columbia St., Seattle, WA 98104) Wyke, J. A.; Vogt, P. K. *Virology* 76(2): 485-493; 1977.

The mutants of avian sarcoma virus (ASV) that are temperature-sensitive (ts) for the induction and maintenance of transformation were studied to identify changes of cellular glycolipid patterns specific for the transformed state. These class T mutants belong to four different "cooperative transformation groups," as defined by their ability to undergo recombination with one another to produce wild-type (wt) sarcoma virus. The mutants are not identical, although they are probably located in the same cistron, the *src* gene. The results of glycolipid analysis in chick embryo fibroblasts (CEF) using chemical and radiolabel quantitation indicate that a three- to fivefold decrease in cellular hematoside concentration is specific in the transformed state. This change was seen in wt virus-infected cultures at 35 and 41 C, but in ts mutant-infected cultures only at 35 C. At the nonpermissive temperature, normal cell morphology and normal hematoside levels are restored. The transformation-dependent reduction in hematoside levels shown could be caused by an increase in sialidase activity or a decrease in synthetase (CMP-sialic acid: lactosylceramide α -sialyltransferase) activity, but efforts to

correlate changes in hematoside level with appropriate enzyme activities have not yet been successful. The higher sialosyl glycolipids of CEF also decrease during transformation, but in mutant-infected cells at the nonpermissive temperature they do not return to normal levels. (31 refs.)

- 77-0883 Distribution and Function of Defined Regions of Avian Tumor Virus Genomes in Viruses and Uninfected Cells.** (Eng.) Varmus, H. E.; Stehelin, D.; Spector, D.; Tal, J.; Fujita, D.; Padgett, T.; Roulland-Dussoix, D.; Kung, H. J.; Bishop, J. M. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 339-358; 1976.

The capability of RNA tumor viruses to cause a variety of tumors in a variety of animals and to transform cells efficiently in culture was investigated, as was the presence of genes related to or identical to viral genes in the DNA of normal cells. Radioactive nucleic acid hybridization reagents specific for genetically or structurally defined regions of the genome of avian RNA tumor viruses (ATV) were prepared and used. The reagents were used to investigate the taxonomy of ATV, the presence of nucleotide sequences resembling these regions in the DNA of normal birds, the evolution of such sequences during avian speciation, the expression and function of the sequences in uninfected cells, and the mechanism of association to form ATV. The reagents are cDNA-sarc, DNA complementary to sequences required for transformation by ASV for sarcoma viruses; cDNA_{gp} for sequences responsible for synthesis of envelope glycoproteins; and cDNA_{3'} for sequences adjacent to the poly(A) region at the 3' of viral RNA. All three sets of sequences can be identified in many virus strains and in the normal chicken genome; the sarc sequences, in contrast to the gp sequences, are highly conserved among avian species, and they are transcribed into RNA under a wide variety of conditions. The findings have implications for theories of the origins of RNA tumor viruses. (47 refs.)

- 77-0884 Production of Large Amounts of 35S RNA and Complementary DNA from Avian RNA Tumor Viruses.** (Eng.) Smith, R. E. (Dept. Microbiology, Duke Univ. Medical Center, Durham, NC 27710) Nebes, S.; Leis, J. *Anal Biochem* 77(1): 226-234; 1977.

The production of RNA (sedimentation constant 35 S) and complementary DNA from avian RNA tumor viruses is described. Ten roller culture bottles of the subgroup C Prague strain of Rous sarcoma virus-transformed chick embryo fibroblasts were harvested every 2 hr for a period of 30 days. Supernatant fluids were collected every 24 hr. Virus production increased during the first wk of culture, reached its max during the second and third wk, and declined during the fourth wk. The total virus obtained was 115.2 mg after iso-

pycnic gradient centrifugation and, on the same 12 days, 224.0 mg of virus were estimated to be present by optical density measurement of the raw pellets. Over the 30-day harvest period, a total of 519 mg of virus was estimated to be present in the raw pellets, or approx 265 mg of purified virus. There were approx 8.7×10^9 cells at the end of the 30-day culture. When the estimated daily yield of cells was combined with the number of cells present at the end of the experiment, it could be seen that approx 18×10^9 cells were produced from 10 roller culture bottles initially seeded with 10^9 cells. Virus 60S RNA prepared by proteinase K treatment contained greater than 80% intact 35S RNA subunits when analyzed by sedimentation through an 80% dimethylsulfoxide-sucrose gradient. In contrast, RNA, prepared without proteinase K digestion, contained relatively small amounts of 35S RNA with the bulk of the RNA sedimenting with values less than 35S. Since ribonuclease remained associated with 60S RNA after sodium dodecyl sulfate-phenol deproteinization in the absence of proteinase K digestion, 60S RNA was prepared with proteinase K treatment. No degradation of the 32 P-labeled RNA was noted after heat denaturation (70 C for 2 min) and analysis by polyacrylamide gel electrophoresis. Incubation of 60S RNA for 30 min at 38 C in the presence of 10 mM magnesium chloride indicated no ribonuclease activity. DNA complementary to the genome of a nontransforming avian leukosis virus contained transcripts greater than 4,500 nucleotides in length; it was prepared by utilizing endogenous reverse transcriptase and proteinase K digestion. Large quantities of undegraded 35S RNA can be obtained by extraction of the virus RNA with the aid of proteinase K. (26 refs.)

- 77-0885 In Vitro Transformation of Specific Target Cells by Avian Leukemia Viruses.** (Eng.) Graf, T.; Royer-Pokora, B.; Beug, H. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 321-338; 1976.

The mechanisms underlying the specificity of the oncogenicity of myeloid and erythroid leukemia viruses are described. There is evidence that there are mechanisms acting at both the cellular and whole-animal levels. Bone marrow cultures were obtained from 2- to 8-wk-old Spafas chicks, and chick embryo cell cultures were prepared from 10-day-old embryos of the same flock. Bone marrow cells transformed in vitro by 10^5 units of avian myelocytomatosis virus strain 29 (MC29) and avian erythroblastosis virus (AEV) had the properties of myeloid and erythroid cells, respectively. The hemopoietic target cells for MC29 virus could be separated from the target cells for AEV on the basis of their adherence and phagocytic ability, indicating they belong to the myeloid, granulopoietic, lineage of differentiation. AEV transformed fibroblasts in addition to hemopoietic cells. Iv injection of cloned AEV induced erythroblastosis only, but im injection induced erythroblastosis and sarcomas. A model is given to explain the results. (12 refs.)

77-0886 Different States of Avian Myeloblastosis Virus DNA Polymerase and Their Binding Capacity

Primer tRNA^{Trp}. (Eng.) Grandgenett, D. P. (Inst. Molecular Virology, St. Louis Univ. Medical Center, St. Louis, MO 63110) Vora, A. C.; Faras, A. J. *Virology* 75(1): 1-32; 1976.

The capacity of $\alpha\beta$ DNA polymerase to bind selectively to avian oncornavirus tRNA^{Trp} (trypsinized transfer RNA), a primer RNA involved in the in vitro synthesis of viral-specific DNA, was investigated. Using 1,4 dioxane to dissociate the $\alpha\beta$ DNA polymerase of avian myeloblastosis virus (BAI Strain A), the three enzyme species α , $\alpha\beta$, and Peak III (enriched with β) were isolated by phosphocellulose chromatography. As demonstrated by its inability to exclude tRNA^{Trp} on Sephadex G-75 columns, α DNA polymerase did not bind significantly to ³²P-tRNA^{Trp}, even when present at a 1000-fold molar excess over the primer RNA, whereas Peak III and $\alpha\beta$ formed a tight complex with tRNA^{Trp}. With the α species, the elution profile of primer was not affected if RNA was chromatographed in the absence or presence of MgCl₂ or MnCl₂. With $\alpha\beta$ and Peak III, MgCl₂ or MnCl₂ were not necessary for binding to occur at 0 C; in the presence of MgCl₂, the amount of excluded tRNA decreased for both enzymes. Peak III and $\alpha\beta$ DNA polymerase also increased the sedimentation rate of tRNA^{Trp} in glycerol gradients. These results indicate that the β subunit in the polymerase is necessary for the holoenzyme to bind tRNA^{Trp} effectively. (9 refs.)

77-0887 Restricted Addition of Proviral DNA in Target Tissues of Chickens infected with Avian Myeloblastosis Virus. (Eng.) Baluda, M. A.; Shoyab, M.; Ali, M.; Markham, P. D.; Drohan, W. N. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, S.; Moloney, W. C., eds. (Munich: J. F. Lehmanns Verlag): p. 311-325; 1976.

The addition of proviral DNA in target tissues of chickens infected with avian myeloblastosis virus (AMV) (BAI Strain A) is reported. RNA hybridization studies investigating the distribution of vertically transmitted endogenous viral DNA in various tissues of normal chickens and the distribution of AMV provirus in various tissues of chickens that developed neoplasias after infection with AMV were conducted. After the injection of AMV into 1-day-old chicks, AMV-specific DNA appeared to be acquired only by tumor cells and by target cells in leukemic chickens. Leukemic myeloblasts, RBC, and the kidneys from leukemic chickens showed about a twofold increase in template DNA. These tissues are known to contain target cells which can be converted to neoplastic cells by AMV. The target cells acquire 1-2 copies of AMV-specific DNA per haploid genome in addition to the endogenous template DNA. The kinetics of hybridization of AMV RNA with DNA from tissues of leukemic chickens varied

with different tissues, and maximum hybridization was obtained with DNA from leukemic myeloblasts or RBC (64-67%). Hybridization obtained with kidney DNA was about 10% lower than with DNA from leukemic myeloblasts or RBC. DNA from muscle or brain hybridized 33% of the input viral RNA, the same fraction of RNA hybridized by DNA from uninfected chickens. It remains unknown whether the newly added viral DNA is alone responsible for neoplastic changes or does so in conjunction with endogenous viral information. (34 refs.)

77-0888 Comparative Effects of Host and Viral Factors on Early Pathogenesis of Marek's Disease.

(Eng.) Fabricant, J. (Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY 14853) Ianconescu, M.; Calnek, B. W. *Infect Immun* 16(1): 136-144; 1977.

The early pathogenesis of Marek's disease (MD) was studied in a series of experiments, each of which involved a single variable (age, genetic strain, or virus strain). Virus assays and fluorescent antibody (FA) tests were conducted from days 3 to 10 after inoculation. With few exceptions, none of the variables tested exerted any appreciable influence on the rate of virus growth in the spleen, bursa, or thymus during the early period (4-6 days). Significant differences were noted in both viral growth rates and FA scores of viral antigen during the late period (8-10 days). These differences generally were correlated with the occurrence of clinical MD in test samples of birds held until 5 wk after infection. There was a significantly higher virus titer in the spleens and buffy coat of the highly susceptible S-strain chickens than in those of the resistant N-line chickens. There were also significantly higher virus titers in chickens infected with the highly virulent GA-5 strain than in those infected with the moderately virulent JM-10 or weakly virulent CU-2 strains of MD virus. These findings support the idea that the basis for resistance or susceptibility (probably immunological response) is common to all of the variables studied. (27 refs.)

77-0889 Isolation from a Transmissible Lymphoid Tumour (TLT) Lymphoblastoid Cell Line of a Herpesvirus Similar to Marek's Disease Virus. (Eng.) Nazerian, K. (US Dept. Agriculture, ARS, Regional Poultry Res. Lab., 3606 E. Mount Hope, East Lansing, MI 48823) Lee, L. F.; Witter, R. L. *Int J Cancer* 19(3): 396-402; 1977.

A chicken lymphoblastoid cell line (TLT-6855) originally established from an avian oncornavirus-induced lymphoma was studied for the presence and expression of Marek's disease virus (MDV) genome. Electron microscopy showed that a large number of C-type virus particles were produced by the cells, but no herpesvirus particles were found. TLT-6855 cells examined by indirect immunofluorescence failed to show MDV-specific antigens or the MD-associated tumor-

specific surface antigen (MATSA). MDV-specific antigens could not be activated by treatment with iododeoxyuridine. The TLT-6855 cells, however, contained a significant amount of DNA sequences hybridizable with MDV-specific ^3H -complementary RNA. When chickens were inoculated with the TLT-6855 cell line, a herpesvirus was repeatedly isolated from the kidneys. Immunofluorescence studies indicated that this herpesvirus was antigenically similar to MDV but was low in oncogenicity for chickens. These observations indicate that a cell line may be positive for the genetic information of both an RNA and a DNA tumor virus. The data also suggest that TLT-6855 cells are transformed by the RNA tumor virus, because the MDV genome present is nononcogenic and the cell line is negative for MATSA, the surface antigen specific to cells transformed by MDV. (16 refs.)

- 77-0890 Immunologic Characteristics in Relation to High and Low Leukemogenic Activity of Radiation Leukemia Virus Variants.** (Eng.) Haran-Ghera, N. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel) Ben-Yaakov, M.; Peled, A. *J Immunol* 118(2): 600-606; 1977.

Infection of adult C57BL/6 mice with variants of the radiation leukemia virus RadLV resulted in variable leukemia incidence. One variant induced lymphatic leukemia in 0 to 25% of mice after inoculation into the thymus of young adult mice. The leukemia incidence was increased to 80 to 100% by host exposure to x-rays (400 R whole-body irradiation). This variant was designated "D-RadLV" because its leukemogenic activity is radiation-dependent. The second variant, A-RadLV (autonomous), induced lymphatic leukemia in 80 to 100% of similarly inoculated mice not given radiation treatment. Adult mice were inoculated with D-RadLV or A-RadLV. Both variants reduced the immune response to sheep RBC. Only D-RadLV had an immunosuppressive effect after immunization with a thymus-independent immunogen polyvinyl-pyrrolidone (PVP). A-RadLV caused impairment of thymus cells and a high leukemia incidence in C57BL/6 mice, but only low leukemia incidence and marrow-cell impairment in (BALB/c x C57BL/6) F_1 mice. T-cells were affected by A-RadLV since their immunocompetent function was impaired. D-RadLV affected the marrow cell population of immunocytes. Exposure of D-RadLV-inoculated mice to x-rays induced functional impairment of both thymus and marrow cells. Since RadLV specifically induces "T" lymphatic leukemia it could be that the initial tropism of the virus to thymocytes would lead to high leukemia induction potential, whereas virus tropism to bone marrow cells would yield a low leukemia incidence. The leukemogenic effect of x-rays could be related to its capacity to alter virus-lymphoid cell interaction. (24 refs.)

- 77-0891 Marek's Disease: Effects of B Histocompatibility Alloalleles in Resistant and Susceptible Chicken Lines.** (Eng.) Briles, W. E. (Dept. Biological

Sciences, Northern Illinois Univ., Dekalb, IL 60115) Stone, H. A.; Cole, R. K. *Science* 195(4274): 193-195; 1977.

In an investigation of Marek's disease, the effects of B histocompatibility alloalleles in resistant and susceptible chicken lines are studied. Chicks were produced in eight biweekly hatches and placed in Horsfall-Bauer isolators. They were inoculated ip at 2 wk of age with 0.2 ml of whole blood infected with Marek's disease virus (JM strain; 2,000 plaque-forming units). Blood was typed at 25 days of age to determine the B genotype of each individual, and the chickens were observed for the presence of Marek's disease through 20 wk of age. The data resulting from each of the separate hatches were pooled for each of the four F_1 parents ($B^{19}B^{21}$) used in matings 628 through 631. One F_1 female (NP, produced by crossing the line N male with a line P female) was backcrossed to line P (mating 628) and produced 12 chicks of genotype $B^{19}B^{19}$, of which 7 died of Marek's disease, and 17 chicks of genotype $B^{19}B^{19}$, of which 2 died of the disease. Similarly, a second F_1 female (PN), backcrossed to line P (mating 629), produced 25 $B^{19}B^{19}$ chicks, of which 20 died, and 18 $B^{19}B^{21}$ chicks, of which 3 died. Backcross progeny were also obtained from two F_1 (PN) males. A high proportion of $B^{19}B^{19}$ and a low proportion of $B^{19}B^{21}$ chicks died of the disease: 24 of 32 $B^{19}B^{19}$ and 2 of 24 $B^{19}B^{21}$ from mating 630 died, while 18 of 30 $B^{19}B^{19}$ and none of 22 $B^{19}B^{21}$ from mating 631 died. The relative incidence of Marek's disease for the two genotypes in each of the four matings was essentially the same. The mortality from Marek's disease for a total of 99 $B^{19}B^{19}$ and 81 $B^{19}B^{21}$ chicks from the 4 F_1 parents was 69.7 and 8.6%, respectively. The incidence of the disease among chicks of genotype $B^{19}B^{19}$ was approx eightfold that among those of genotype $B^{19}B^{21}$. The data suggest that the high degree of resistance to herpesvirus tumorigenesis in individual chickens possessing the B^{21} alloallele results from cell-mediated immunity. (46 refs.)

- 77-0892 Immunologic Characteristics in Relation to High and Low Leukemogenic Activity of Radiation Leukemia Virus Variants: II. Analysis of the Immune Response.** (Eng.) Haran-Ghera, N. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel) *J Immunol* 118(2): 607-611; 1977.

The immune responses induced by two variants of the radiation leukemia virus having high (A-RadLV) or low (D-RadLV) leukemogenic potential were compared. Effective immunization could be induced only with RadLV variants having low leukemogenic potential when injected into adult mice of specific strains (D-RadLV in C57BL/6 mice and A-RadLV in (BALB/c x C57BL/6) F_1 mice). Immunologic cross-reactivity among the RadLV variants and the leukemic cells induced by them was demonstrated in several systems. Transplantation resistance could be induced in certain strains against challenge of leukemic cells by a 1:1 mixture of both RadLV variants. Isoantisera, raised in the suitable strains, could neutralize the leukemogenic activity of both A-RadLV and D-RadLV. Leukemic cells induced by each of the vari-

ants shared cell-surface antigens. Circulating anti-tumor antibodies, induced by either variant in the appropriate strains, efficiently lysed the target leukemic cells. These results suggest that antibodies have an important role in the control of virus- and/or leukemic-cell proliferation. (12 refs.)

77-0893 Host Restriction of Friend Leukemia Virus: Proteins and Messenger RNA. (Eng.) Soeiro, R.; Sveta, M. M.; Krontiris, T. G.; Ray, U. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 257-268; 1976.

The mechanism of Fv-1-induced host restriction, particularly late events in the viral replication cycle, was investigated. Murine oncornavirus host restriction is multigenic, and only the host gene Fv-1 controls the ability of particular oncornaviruses to replicate in tissue culture or produce leukemia. Total and viral envelope synthesis was studied to determine whether the Fv-1 gene effect was at the level of control of translation or assembly of viral proteins. In addition, the amounts of viral-specific messenger RNA (mRNA) in the cytoplasm and nucleus of the infected cell were determined. The results do not indicate directly the site of the Fv-1 gene effect on the replication of Friend leukemia virus. They suggest that the site of action is early, perhaps at synthesis or integration of the provirus, or at its transcription. Since there are no cell-associated viral proteins present, it is concluded that the host-restriction phenomenon does not act at the level of viral assembly. Analysis of the proteins shows no evidence of a faulty processing of viral precursor proteins. Decreases in viral-specific functioning mRNA suggest that the host-restricting effect is not due to inhibition of the translation of viral mRNA. (16 refs.)

77-0894 Isolation of a Fibroblast Nonproducer Cell Line Containing the Friend Strain of the Spleen Focus-forming Virus. (Eng.) Troxler, D. H. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014) Parks, W. P.; Vass, W. C.; Scolnick, E. M. *Virology* 76(2): 602-615; 1977.

Two single cell clones that contain spleen focus-forming virus (SFFV) free of replicating C-type helper virus, lymphatic leukemia virus (LLV), were isolated by infection of BALB/c 3T3 cells with an appropriate dilution of BALB/c spleen homogenate. This homogenate apparently had an LLV:SFFV ratio of approx 2:1. The nonproducer clone cells contain the SFFV genome, but are virus-negative under electron microscopy and do not release virus particles. They are also of a similar morphology to uninfected BALB/c 3T3 cells. If the SFFV free of LLV was superinfected with LLV, the resulting mixture yielded the usual splenic foci in weanling or adult BALB/c mice. It appears then that SFFV is like mammalian RNA-containing sarcoma viruses in being unable to transform mouse fibroblasts, being replication-defective, but being still associated with a malignant disease. (39 refs.)

77-0895 Spontaneous Regression of Friend Virus-induced Erythroleukemia. I. The Role of the Helper Murine Leukemia Virus Component. (Eng.) Dietz, M. (Dept. Biology, Michigan Cancer Foundation, Detroit, MI 48201) Fouchey, S. P.; Longley, C.; Rich, M. A.; Furmanski, P. *J Exp Med* 145(3): 594-606; 1977.

Factors responsible for the spontaneous regression of Friend virus (FV)-induced erythroleukemia were investigated. The tropism of regressing FV complex (RFV), which is conferred by its helper murine leukemia virus (MuLV) component, MuLV-RF, is different from that of the conventional virus strain, CFV. Passage of nonregressing CFV through Fv-1-incompatible Swiss/ICR mice changed the tropism of CFV from N to NB and gave a virus strain that induced erythroleukemia that regressed. Altering the quantity or type of MuLV in RFV by addition of Rich murine leukemia virus (Ri-MuLV) inhibited regression in proportion to the amount of added Ri-MuLV. MuLV-RF isolated from the RFV complex induced lymphocytic leukemia in newborn mice that regressed and caused the regression of CFV-induced erythroleukemia. Pseudotype viruses, consisting of MuLV-RF or other MuLV's and spleen focus-forming virus (SFFV) derived from B-tropic FV complex, each acquired the tropism of the MuLV used in rescue. The pseudotype prepared with MuLV-RF or another NB-tropic MuLV-F, but not the virus obtained by rescue with N-tropic MuLV-F, induced erythroleukemia that spontaneously regressed. It is concluded that the ability of RFV to induce spontaneously regressing erythroleukemia is due to its helper MuLV component. (31 refs.)

77-0896 Analysis by Computer-controlled Cell Sorter of Friend Virus-transformed Cells in Different Stages of Differentiation. (Eng.) Arndt-Jovin, D. J. (Abteilung Molekulare Biologie, Max-Planck-Institut für biophysikalische Chemie, Postfach 968, D-3400 Göttingen, W. Germany) Ostertag, W.; Eisen, H.; Jovin, T. M. *Haematol Bluttransfus* 19: 137-149; 1976.

A computerized cell separator was used to study three cell surface phenomena during different stages of chemically-induced differentiation among mouse spleen cells transformed originally with Friend erythroleukemia virus. The mobility of lectin binding sites for concanavalin A (Con A) on Friend virus transformed cells appeared to change during the first day of chemically-induced differentiation (1% dimethylsulfoxide (DMSO)), as measured by the increased agglutinability of the cells, and coincided with a decrease in membrane permeability 6 hr after DMSO addition. However, measurements of the number of binding sites for lectin, assayed both by the binding of ¹²⁵I-iodine-labeled Con A and by the fluorescence of bound fluoresceinated Con A, indicated that no net increase in the number of lectin binding sites occurred until later in differentiation. Mature mouse RBC showed fewer H-2 histocompatibility antigen sites when living cells tagged with fluorescent antibody were measured and

sorted in the cell separator. The mean signal size of the fluorescent cell population decreased with time after induction of the cultures by DMSO. Friend virus transformed cells induced with DMSO also appeared to have increasingly rigid membranes as indicated by an increasing anisotropy of the dye 1,6-diphenyl-1,3,4-hexatriene in the cell membranes that correlated with time after cell differentiation induction. It appears that flow systems capable of separating cells on the basis of spectroscopic properties are not only useful for the study of controlled cell differentiation and transforming viruses but may also be useful for the diagnosis of leukemia, of preleukemic states, and of leukemic relapse. (34 refs.)

- 77-0897 Use of Silica to Identify Host Mechanisms Involved in Suppression of Established Friend Virus Leukemia.** (Eng.) Wirth, J. J. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA 19107) Levy, M. H.; Wheelock, E. F. *J Immunol* 117(6): 2124-2130; 1976.

The utilization of silica to identify host mechanisms involved in suppression of established Friend leukemia virus (FLV) is investigated. Silica given 3 days before FLV did not have a significant effect on leukemiosuppression by chlorite-oxidized oxyamylose (COAM)-statolon. Silica given 1 day before or 1 day after FLV significantly inhibited leukemiosuppression. However, the inhibitory effects of silica on leukemia suppression were greatest when silica was given 2 or 3 days after FLV infection. Silica administered 1 day after FLV did not significantly alter the amount of interferon detected in the serum after COAM-statolon treatment. Adoptive transfer of FLV-immune spleen cells resulted in FLV antibody production and FLV leukemiosuppression in recipient DBA/2 mice. To determine the role of COAM-statolon-induced interferon in FLV leukemiosuppression, the leukemiosuppressive effects of transferred FLV-immune spleen cells were compared in three groups of recipient mice. The FLV-infected recipient mice were untreated, treated with silica alone, or treated with silica and COAM-statolon. The leukemiosuppressive effects of 8×10^7 transferred FLV-immune spleen cells were decreased from 75 to 43% when FLV-infected mice were treated with silica. The same number of FLV-immune cells transferred to FLV-infected mice that had been treated with silica and COAM-statolon suppressed leukemia in 100% of the recipients. Transfer of fewer (8×10^6) FLV-immune cells to either FLV-infected untreated mice, or to FLV-infected, silica-treated mice did not suppress leukemia. However, transfer of 8×10^6 FLV-immune cells to FLV-infected, silica-treated mice that had also received COAM-statolon significantly suppressed leukemia (33%). The nonadherent FLV-immune spleen cells were leukemiosuppressive (71% dormant FLV infections) but to a lesser degree than untreated (silica and COAM-statolon) spleen cells (100%). The theta antigen-bearing T cells participated in adoptive immunotherapy of FLV erythroleukemia. Depression of immune responsiveness to FLV antigens seems to be the major cause of silica's inhibitory effects on COAM-statolon-induced FLV leukemiosuppression. (44 refs.)

- 77-0898 Early and Late Volume Changes During Erythroid Differentiation of Cultured Friend Leukemic Cells.** (Eng.) Loritz, F. (Dept. Medical Biophysics, Univ. Toronto, Toronto, Ontario, Canada) Bernstein, A.; Miller, R. G. *J Cell Physiol* 90: 423-438; 1977.

The volume changes that occur in populations of Friend erythroleukemic cells (FLC) stimulated to differentiate with dimethyl sulfoxide (DMSO) were characterized. FLC line 745A; a thioguanine-resistant mutant cell line; FTG, which does not induce in DMSO; and an α -amanitin-resistant line, Ama-2B, which is weakly inducible in DMSO, were the cells employed. Chinese hamster ovary (CHO) cells were used as nonerythroid dimethylacetamide (DMA), 80 mM ethylurea (EU), 80 mM urea (U), and 40 mM pyridine-N-oxide (PNO). Procaine (PRO 1 mM) was used to block induction in several experiments. The earliest change accompanying the induction of FLC by chemical agents was a decrease in the modal cell volume after 10 hr. The extent of the early volume shift was proportional to the dose of DMSO. The volume change was shown to be cell-cycle-dependent by the addition of the mitotic inhibitor, colcemid, to the cultures. Cell-cycle dependence was also demonstrated by the volume spectra of exponentially growing cells divided into G₁, S, and G₂-M subpopulations. The results suggest that exposure to DMSO during the S phase must be followed by one round of mitosis for expression of a volume change. In FLC that had begun to produce Hb, a progressive reduction in cell size was observed after 2-3 days exposure to DMSO. The volume coefficient of variation increased as the cell culture became more heterogeneous with respect to cell size. The modal volume decreased by up to 50% at day 5 in cultures that developed > 50% benzidine-positive cells. (32 refs.)

- 77-0899 Reduced Transplantability of Syngeneic Mouse Tumors Superinfected with Membrane Viruses in Nu/Nu Mice.** (Eng.) Kuzumaki, N. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden) *Transplantation* 22(6): 545-550; 1976.

The decreased transplantability of syngeneic mouse tumors superinfected with membrane viruses in nu/nu mice is evaluated. Fibrosarcomas were induced by methylcholanthrene. The sc growth rate of 5×10^6 Meth A cells superinfected with Friend lymphatic leukemia virus (LLVF) in virus-infected BALB/c mice was compared with that of the uninfected identical tumor in syngeneic mice. The LLVF-infected Meth A tumor grew more slowly than the uninfected tumor, although no difference in total takes was noted. However, the retardation of growth in virus-infected Meth A tumor was not observed in mice that had been given injections of LLVF at birth. BMT-7 superinfected with LLVF in virus-infected C57BL/6 mice also grew more slowly than uninfected BMT-7 in syngeneic hosts. The delay of growth was not found in mice given neonatal injections of LLVF. The sc growth of syngeneic tumor superinfected with Moloney murine sarcoma virus (MSV-M), endogenous rat leukemia virus

RaLV), or human measles virus (HMV) in nu/nu mice was studied in normal syngeneic mice and compared with that of uninfected tumors. Meth A (5×10^6) or MH134 (1×10^6) cells superinfected with MSV-M in nu/nu mice grew more slowly than their respective syngeneic hosts, and some of them regressed, while uninfected tumors grew rapidly and progressively. MSV-M infected tumors were implanted into mice immunodepressed with 350 rads of x-irradiation 24 hr before tumor challenge. The Meth A and MH134 superinfected with MSV-M grew rapidly and eventually killed all the irradiated mice. No prolongation of survival period was noted. In addition, 5×10^6 of Meth A cells superinfected with RaLV and 1×10^6 of MH134 cells superinfected with HMV in nu/nu mice also demonstrated reduced transplantability as compared with uninfected tumors. Three out of 12 RaLV-infected Meth A cells were rejected by normal syngeneic hosts. A spontaneous leukemia in C57BL/6 mice, C1498 cells superinfected with MSV-M in nu/nu mice did not show reduced transplantability in normal syngeneic hosts. Appropriate combinations between virus, tumor, and host have to be found for successful reduction in transplantability of malignant tumors. (18 refs.)

The conversion of exogenous virus into endogenous virus with Moloney murine leukemia virus (M-MuLV) by infecting BALB/129 newborn mice or preimplantation mouse embryos at the 4- to 8-cell stage is described. Both newborns and embryos developed an M-MuLV-induced leukemia. Mendelian transmission of M-MuLV occurred in the progeny of the sons, grandsons, and great grandsons of the infected animal. It was possible to calculate from the data that one-half copy of M-MuLV per haploid, or one copy per diploid, mouse genome equivalent is present in the "nontarget" organs of viremic N-1- and N-2-generation animals. During leukemogenesis the number increases to a max of two copies per haploid mouse genome. The data strongly suggest that subsequent generation animals are heterozygous for one locus responsible for M-MuLV synthesis. In additional experiments, a study was made of leukemogenesis in AKR mice that carry the endogenous Gross-MuLV in their germ line, to see whether the leukemia is accompanied by an increase in the number of AKR virus-specific genes in the tumor tissues. AKR virus-specific sequences were amplified in the "target" cells of leukemic AKR mice, but not in the "nontarget" cells. (31 refs.)

7-0900 **The Use of Vesicular Stomatitis Virus Pseudotype Production in the Study of a Temperature-Sensitive Murine Leukemia Virus.** (Eng.) Breitman, M. Dept. Biology, McMaster Univ., Hamilton, Ontario, Canada. a) Prevec, L. *Virology* 76(2): 643-652; 1977.

A Moloney murine leukemia virus (MLV-M) mutant, designated ts, and grown on TB cells (a continuous line established from the bone marrow and thymus of CFW/D mice), has a temperature-sensitive defect that prevents the release of budding virus particles. The formation of pseudotypes between this virus and vesicular stomatitis virus (VSV) was investigated at permissive and nonpermissive temperatures for ts, to show whether the defective function resides in an envelope component of the virion. The results indicate that phenotypic mixing between VSV and ts, is temperature-dependent. Further temperature-shift experiments indicate that two separate blocks to VSV(ts,) pseudotype production may occur as a function of the length of time ts,-infected cells are incubated at the nonpermissive temperature. The lack of pseudotype formation probably arises from a sequestering ts, envelope protein, as ts,-infected cells, preincubated for 24 hr at 39 C, gradually became competent for VSV(ts,)-pseudotype formation upon shifting to the permissive temperature. (13 refs.)

77-0902 **Infection of Developing Mouse Embryos with Murine Leukemia Virus: Tissue Specificity and Genetic Transmission of the Virus.** (Eng.) Jaenisch, R. (Salk Inst., San Diego, CA 92112) Dausman, J.; Cox, V.; Fan, H.; Croker, B. *Haematol Bluttransfus* 19: 341-356; 1976.

The tissue specificity of Moloney leukemia virus (M-MuLV) was studied by infecting BALB/c mice at two different stages of development. Either newborn mice, which can be considered as fully differentiated animals, were infected with M-MuLV or preimplantation mouse embryos were infected in vitro at the 4-8 cell stage, a stage of development before differentiation has occurred. After surgical transfer of the embryos to the uteri of pseudopregnant surrogate mothers, the latter developed to term and adult mice. In both cases, animals were obtained that had developed an M-MuLV induced leukemia. Molecular hybridization tests for the presence of M-MuLV-specific sequences revealed that mice infected as newborns carried M-MuLV-specific sequences in target tissues only, ie, thymus, spleen, lymph nodes, or organs infiltrated by tumor cells. In contrast, when leukemic animals derived from M-MuLV-infected preimplantation embryos were analyzed, virus-specific sequences were detected in both target tissues and nontarget tissues such as the liver, kidney, brain, testes, and germ line. RNA was extracted from different tissues of an animal infected at the preimplantation stage to study the expression of the viral DNA integrated in target and nontarget organs, and 50-100 X more M-MuLV-specific RNA was detected in tumor tissues than was found in nontarget organs. Since all organs contained the same amount of virus-specific DNA, the integrated virus genome can apparently be differentially expressed in different tissues. Mice infected at the preimplantation stage had M-MuLV integrated into their germ line. Virus transmission from the father to

7-0901 **Germ Line Integration and Leukemogenesis of Exogenous and Endogenous Murine Leukemia Viruses.** (Eng.) Jaenisch, R.; Berns, A.; Dausman, J.; Cox, V. In: *Animal Virology. ICA-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. eds. (New York: Academic Press, Inc.): Vol. 4, pp. 283-310; 1976.

the offspring occurred according to simple Mendelian expectations. Molecular hybridization tests revealed that the virus was integrated into the germ line at only one out of two or three possible integration sites. During the development of leukemia, amplification of this virus copy was observed in the target tissues only and not in nontarget tissues. (25 refs.)

- 77-0903 Cellular Maturation of Oncornavirus Glycoproteins: Topological Arrangement of Precursor and Product Forms in Cellular Membranes.** (Eng.) Witte, O. N. (Lab. Experimental Oncology, Dept. Pathology, Stanford Univ. School Medicine, Stanford, CA 94305) Tsukamoto-Adey, A.; Weissman, I. L. *Virology* 76(2): 539-553; 1977.

The intracellular lineage of the major virion glycoproteins (gp69, 71) of Moloney sarcoma-leukemia virus (MSV-MLV) and its maturation in membrane assembly are described. Cell precursors of gp69,71 appear rapidly after synthesis, in association with a high-density membrane glycoprotein (gp80) of 80,000-85,000 molecular wt and an isoelectric range of pH 6.6-6.8. Species gp80 passes through the cell membrane systems to the plasma membrane, where it is converted to gp69,71. The transition requires sialidation and proteolytic cleavage, resulting in membrane heterodimers of p14-gp69, 71 covalently bound by disulfide linkages. Pulse-chase and other data have not detected intermediates between gp80 and gp68,71. Only gp69, 71 is incorporated into budding virions. Both gp80 intracellular precursor forms and enzyme-accessible gp69,71 membrane forms are present in large pools, compared to core polypeptides. Transition of gp80 to gp69,71 involves both a displacement to the plasma membrane and simultaneous uncovering of a recognition site on the inner aspect of the membrane for viral budding. It is not known if submembrane core formation follows random lateral association of gp69,71 forms in the membrane plane or if core formation is a site for gp69,71 nucleation. The gp80 forms have a long intracellular life and are mainly associated with rough endoplasmic reticulum and Golgi membranes. (43 refs.)

- 77-0904 Virus-Induced Animal Model of Osteosarcoma in the Rat. Morphologic and Biochemical Studies.** (Eng.) Olson, H. M. (Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Ohio State Univ., 1925 Coffey Road, Columbus, OH 43210) *Am J Pathol* 86(2): 437-458; 1977.

A virus-induced animal model of osteosarcoma in the rat is presented. Osteosarcomas were produced by the intratibial inoculation of New Zealand black rats at 4 days and 1 day of age with Moloney sarcoma virus. Initiation and development of osteosarcomas in rats inoculated with virus at 1 day of age were noted as early as 10-12 days postinfection (11/12 rats). Rats inoculated at day 4 after birth developed palpable and/or radiographic evidence of tumor development as early as the 12th day after inoculation. Most tumors were palpable

by day 15 postinfection (6/8 rats). Tumor-bearing rats inoculated at 4 days of age lived significantly longer than rats inoculated at 1 day of age. Neoplasms in rats inoculated with the virus on day 1 were radiolucent tumors with fine interspersed radiodense spicules. Rats inoculated with virus on day 4 after birth developed more uniformly radiodense osteosarcomas with only small lucent zones. Histologic evaluation of sublumbar lymph nodes and lungs revealed 17/18 rats inoculated at day 1 and 13/14 tumor-bearing rats inoculated at day 4 had metastatic lesions. Ultrastructural evaluation of osteosarcomas from rats inoculated at 4 days of age revealed many well-differentiated osteoblasts surrounded by a fibrillar osteoid stroma with a mineralization front. C-type viral particles were often observed budding from the plasma membranes of all types of cells within the osteosarcomas. Four-day-old rats inoculated with the virus developed significant elevations of serum calcium and alkaline phosphatase levels. Conversely, significantly elevations in both parameters were noted infrequently in rats inoculated 1 day after birth. Urinary hydroxyproline excretion was significantly elevated in both groups of tumor-bearing rats compared to controls at days 25 and 30 postinfection and again at day 70. Sustained high levels of hydroxyproline excretion were noted for rats inoculated at day 4 of age compared to controls. This virus-induced osteosarcoma should be a valuable animal model to study the biological behavior of osteosarcoma. (43 refs.)

- 77-0905 Evidence that MuLV-Induced Thymic Lymphoma Cells Possess Specific Cell Membrane Binding Sites for MuLV.** (Eng.) Baird, S. (Lab. Experimental Oncology, Dept. Pathology, Stanford Medical Sch., Stanford CA 94305) Raschke, W.; Weissman, I. L. *Int J Cancer* 19(3): 403-413; 1977.

Cell-surface binding sites specific for thymotropic murine leukemia viruses (MuLV) were detected in high concentrations of thymic lymphoma cell lines induced by MuLV. These binding sites were detectable to a much lower degree, or not at all, on normal thymocytes, spleen cells, and on several murine in vitro non-T-cell lines of hematolymphoid origin. Moloney leukemia virus (M-MuLV) bound specifically to a lymphoma induced by M-MuLV, but not to a thymic lymphoma induced by Gross leukemia virus (G-MuLV). G-MuLV bound to an AKR lymphoma but not to a M-MuLV induced lymphoma. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis indicated that the material that binds to these T-lymphoma membrane sites is input virus, not a contaminant that copurifies with virus. Both autoradiographic and fluorescent virus-binding studies demonstrated that a high proportion of T-lymphoma cells possess binding sites, but only a rare cell in the thymus binds murine leukemia virus to the same degree. It is suggested that there exists within the normal thymus lymphocyte population a subset of cells that bear specific MuLV receptors and that only these cells are susceptible to infection and/or transformation by the MuLV. (31 refs.)

77-0906 Envelope Glycoproteins of Rauscher Murine Leukemia Virus: Isolation and Chemical Characterization. (Eng.) Marquardt, H. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD 21701) Gilden, R. V.; Oroszlan, S. *Biochemistry* 16(4): 710-717; 1977.

The envelope glycoproteins (designated gp70 and gp45) of the Rauscher strain of murine leukemia virus were characterized. The glycoproteins were solubilized by osmotic shock and freeze-thawing in chaotropic soln and purified by phosphocellulose and gel permeation chromatography. The electrophoretic protein patterns of isolated gp70 and gp45 were determined on 10% sodium dodecyl sulfate-polyacrylamide gels. The gels indicated a high degree of homogeneity for both purified glycoproteins. The apparent molecular wt of gp70 decreased asymptotically with increasing gel concentrations, giving a minimal molecular wt of 67,500. The apparent molecular wt of gp45 was independent of the acrylamide concentration. An av molecular wt of 47,500 was calculated as the arithmetical mean of the values obtained from different percentages of acrylamide. Alanine was the amino-terminal amino acid of both gp70 and gp45. Despite the charge heterogeneity of gp70, the protein molecules appeared to be homogenous by N-terminal amino acid analysis. Hexosamines were quantitated on the amino acid analyzer. The glucosamine and galactosamine contents for gp45 were 3.93% and 1.91%, respectively. Other sugars of gp45 were not determined. The amino acid and hexosamine contents accounted for 97.3% of the total gp45 molecule. Complete carbohydrate analyses of gp70 were done on preparations isolated from a sodium chloride extract. Only small amounts of fucose and galactosamine were present. The major components were mannose, galactose, glucosamine, and neuraminic acid. The total carbohydrate content was approx 32%. An immunoelectrophoretic analysis of isolated gp70 and gp45 was performed. The electrophoresis was done in sodium borate buffer, pH 8.6, since the resolution of gp70 in this buffer was superior to that obtained in sodium barbital buffer at the same pH. Both glycoproteins migrated slightly toward the cathode. The asymmetric arc shape of gp70 compared with gp45 in the immunoelectropherogram showed the charge heterogeneity of gp70. The major difference between gp45 and gp70 may lie in the carbohydrate content. (31 refs.)

77-0907 Hormone Independent In Vitro Erythroid Colony Formation by Mouse Bone Marrow Cells. (Eng.) Nooter, K. (Radiobiological Institute TNO, Lange Kleiweg 151, Rijswijk (ZH), Netherlands) Ghio, R.; Berg, K. J.; Bentvelzen, P. A. *Haematol Bluttransfus* 19: 151-159; 1976.

Bone marrow cells from Rauscher murine leukemia virus (RLV) infected BALB/c mice were compared with cells from uninfected mice with regard to their dependency on erythropoietin hormone (EP) for the in vitro development of erythroid colonies. Bone marrow (BM) cells of mice injected ip with RLV proliferated in methylcellulose in the absence of EP, while normal BM cells did not. Three days after infection,

there was a fivefold increase in the number of erythroid colonies formed by the bone marrow of RLV-infected mice not treated with EP. Hormone independence was also observed in terms of erythroid burst forming unit (BFU-E), thought to be a more primitive member of the erythroid series than the erythroid precursor cell (CFU-E). The number of BFU-E after 10 days of culture of BM cells from mice infected with RLV 15 days earlier was 8 in the absence of EP and 21 when EP (1 IU) was added. For mice not infected with RLV, the corresponding BFU-E values were 2 and 17, respectively. Complete Freund's adjuvant (CFA) enhanced RLV-induced erythroblastosis; when BALB/c mice were injected with crude cell-free RLV and with CFA (0.2 ml, ip) on the same day, the number of EP-independent CFU-E was about 260 for bone marrow samples taken 10 days after infection, whereas a value of about 180 was observed for mice not treated with CFA. In vitro transformation experiments involving the induction of hormone-independency by incubation in vitro of normal BM cells with RLV at various dilutions (10-12,800) showed a linear dose-response relationship 5 days after plating, with the number of EP-independent colonies decreasing from $538/2 \times 10^5$ BM cells at an RLV dilution of 10 to $24/2 \times 10^5$ BM cells at a dilution of $3,200 \times$, which seemed to represent an end point. Experiments involving transfection with proviral DNA (50 $\mu\text{g}/\text{ml}$) also resulted in the transformation of CFU-E of BALB/c mice. It appears that RLV-induced erythroblastosis is a true neoplasia, although transplantation experiments have failed thus far. (19 refs.)

77-0908 Biosynthesis and Processing of Rauscher Leukemia Viral Precursor Polyproteins. (Eng.) Arlinghaus, R. B.; Naso, R. B.; Jamjoom, G. A.; Arcement, L. J.; Karshin, W. L. In: *Animal Virology. ICN-UCLA Symposium on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 689-716; 1976.

The synthesis of Rauscher leukemia viral (RLV) structural proteins was studied in RLV-infected NIH Swiss mouse embryo cells and RLV-infected Balb/c mouse spleen and thymus cells. The structural proteins were synthesized by way of high molecular wt precursor polyproteins identified as Prla+b (200,000 daltons), Pr2a+b (90,000 daltons), Pr3 (80,000 daltons), Pr4 (65,000 daltons), Pr5 (55,000 daltons), and Pr6 (45,000 daltons). Tryptic peptide mapping experiments indicated that p30 is contained in precursors Prla+b and Pr3 through Pr6. Viral protein p15 peptide sequences were present in Pr3 through Pr5, and p10 was contained in Pr3 and Pr4, indicating that both p10 and p15 must also originate from Prla+b. Tryptic peptides of viral gp69/71 and p12 were found in Pr2a+b and not in Prla+b. Treatment of infected cells with inhibitors of proteolytic enzymes caused a buildup of Prla+b and prevented the formation of mature structural proteins. A model for the biosynthesis of Rauscher viral proteins is presented in which Prla+b and Pr2a+b are considered primary gene products derived by translation of 35S viral RNA and subsequent nascent chain cleavage. (34 refs.)

- 77-0909 In Vitro Lymphoid Cell Transformation by Abelson Murine Leukemia Virus.** (Eng.) Rosenberg, N.; Baltimore, D. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 311-320; 1976.

The ability of the Abelson murine leukemia virus (A-MuLV) to transform lymphoid cells in vitro was studied in two different transformation systems. Cell suspensions from murine fetal liver or adult bone marrow were infected with A-MuLV and with the Moloney-MuLV helper virus present in the A-MuLV stocks to transform mass cultures of hematopoietic cells. Lymphoid morphology was noted 10-15 days postinfection. The continuous replication of these cells and the production of rapidly invasive tumors by these cells after injection into animals show that they are oncogenic. Approximately 10^8 cells can be isolated 21 days postinfection from the bone marrow of the femurs of one adult mouse. Quantitation of transformation and the study of cells arising from single transformation events were studied in the second system, focus transformation of hematopoietic cells. A semisolid agarose culture assay system was developed to study lymphoid cell transformation at the level of single virus particle-single cell interaction. Cell lines were derived from most foci, and they did not differ from cell lines isolated from the mass cultures with respect to cell morphology or population-doubling time. This assay system has been used to determine the ratio of A-MuLV fibroblast focus-forming units to lymphoid focus-forming units (approx $10^3:1$). (20 refs.)

- 77-0910 Transformation of Cultured Rat Adrenocortical Cells by Kirsten Murine Sarcoma Virus (Ki-MSV).** (Eng.) Auersperg, N. (Cancer Res. Centre, Univ. British Columbia, Vancouver, British Columbia, V6T 1W5, Canada) Hudson, J. B.; Goddard, E.; Klement, V. *Int J Cancer* 19(1): 81-89; 1977.

The transformation of rat adrenocortical cells in primary culture to functional adrenocortical carcinoma by Kirsten mouse sarcoma virus (ki-MSV) is reported. Rapidly proliferating refractile cells began to replace all normal cells in 14-day primary cultures of rat adrenal cells by day 7 after inoculation of Ki-MSV. The doubling time was < 16 hr, compared to 36-40 hr for normal adrenocortical cells. The transformed cells were pleomorphic, epithelial in shape and intercellular relations, and less cohesive than normal cells. Spontaneous hemorrhagic tumors appeared in 1-2 wk after injection of the transformed cells into immunodepressed rats. The tumors were pleomorphic, with areas of anaplastic medullary carcinoma and eosinophilic cells with cytoplasmic vacuolization. The transformed cells also retained the capacity to convert pregnenolone to intermediates of normal adrenocortical steroid metabolism, including progesterone, 20α -dihydroprogesterone, and 20α -dihydropregnenolone. C-type RNA virus particles were found both budding from the cell surface and free in the extracellular space; serological assay confirmed that the

released virus was similar to Ki-MSV. The successful transformation of differentiated secretory epithelial cells by Ki-MSV suggests that the adrenal cortex is ontogenetically mesodermal, although phenotypically epithelial, and eligible for transformation by sarcoma viruses. (22 refs.)

- 77-0911 Expression of Viral Envelope Glycoprotein and Transformation Genes in Cells Transformed by a Defective Kirsten Murine Sarcoma Virus.** (Eng.) Bilello, J. A. (Dept. Molecular Biology, Div. Biological Sciences, Albert Einstein Coll. Medicine, Bronx, NY 10461) Strand, M.; August, J. T. *Virology* 77(1): 233-244; 1977.

The use of interference and host range assays to establish the murine origin of the envelope glycoprotein synthesized by clones of Kirsten-transformed cells that do not produce virus is described. Normal rat kidney (NRK) cells infected with rodent or primate C-type viruses were subjected to superinfection by the Kirsten murine sarcoma/leukemia virus complex (KSV/KMuLV). This virus failed to induce morphological transformation in NRK cells, confirming the group-specific pattern of interference to superinfection. Clones of envelope-positive cells were resistant to superinfection, but (KSV env-)NRK cells were readily infected by ecotropic viruses. In controls, both woolly monkey and murine xenotropic viruses rescued the sarcoma virus genome from both envelope-positive and envelope-negative cells. Sarcoma virus rescued from envelope-positive and envelope-negative transformed cells superinfected with murine and primate viruses were able to transform both murine and rat cells. The expanded host range of the xenotropic murine and primate viruses can be attributed to phenotypic mixing between the virion-coded proteins and the ecotropic Kirsten virus envelope of the (KSV env+)NRK cells. A normally excluded virus genome may enter a resistant cell via phenotypic mixing. (43 refs.)

- 77-0912 Decreased Immunity to Viral Antigens and Increased Expression of Endogenous Leukemia Viruses in Athymic (Nude) Mice.** (Eng.) Nowinski, R. C. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St. Seattle, WA 98104) Doyle, T. *Virology* 77(1): 429-432; 1977.

Diminished immune response to viral antigens was demonstrated in athymic BALB/c mice. Two groups of partially inbred BALB/c mice that were segregating at the nude (nu) locus were obtained. One group was maintained under gnotobiotic conditions and one was maintained under conventional caging conditions. Sera from 29 of the gnotobiotically reared mice were examined by radioimmune precipitation (RIP) assay for antibody against endogenous ecotropic murine leukemia virus (MuLV). Heterozygous (nu/+) segregants produced higher titers of anti-MuLV than their homozygous (nu/nu) littermates. Thirteen of the 14 heterozygotes exhibited high titers of anti-MuLV antibodies

at none of the homozygotes showed any detectable anti-MuLV antibodies. Similar results were obtained with 57BL/6 and BALB/c mice reared conventionally. Gnotobiotically reared BALB/c heterozygotes did not carry detectable MuLV in their sera, but the homozygous (nu/nu) mice did carry infectious MuLV. The hypothesis that this immune response was a result of antigenic stimulation occurring from activated endogenous MuLV is supported by the occurrence of natural immunity in gnotobiotically reared BALB/c mice (nu/+). (9 refs.)

77-0913 A Positive Difference in Nature of Envelopes of Thymus- and Uterus-derived Leukemia Viruses of AKR Mice. (Eng.) Watanabe, T. (Dept. Microbiology, Wakayama Medical Coll., 9-9 Wakayama-Shi 640, Wakayama, Japan) Nakakuki, K. *Can J Microbiol* 23(3): 354-357; 1977.

Thymus-derived leukemia virus (TLV) of 5-mo-old AKR/J mice was inactivated by anti- θ antiserum but not by antiserum that had been absorbed with intact thymus cells of AKR/J or RF/J mice nor by anti-uterus-derived leukemia virus antiserum. Uterus-derived leukemia virus (ULV) was not inactivated by anti- θ antiserum but was by anti-ULV antiserum. The apparent discrepancy between infectivity titers of TLV and ULV and their leukemogenicities might be explained by the difference in the envelopes of these two viruses. Adsorption and penetration of leukemia virus on and into a thymus cell would be expected to be essential steps in thymic lymphoma. Thus TLV, having an envelope that has a common immunogen to the plasma membrane of a thymus cell, could be more leukemogenic than ULV. The findings do not rule out the possibility, however, that ULV has a defective gene in its chromosome that results in less leukemogenicity when it is injected into the thymus of AKR mice. (10 refs.)

77-0914 Expression of Endogenous Murine Leukemia Viruses During the Course of a Protracted Immunological Disorder. (Eng.) Armstrong, M. Y. (Dept. Epidemiology, Yale Univ. Sch. Medicine, New Haven, CT 06510) Ruddle, N. H.; Richards, F. F. *J Exp Med* 145(4): 1060-1065; 1977.

The expression of oncogenic potential of murine leukemia virus (MuLV) in male (BALB/cJ \times A/J)F₁ hybrid (CAF₁) mice during the course of graft-versus-host reaction (GVHR). Spleen cell suspensions from GVHR-CAF₁ mice, normal uninjected CAF₁ mice, and normal uninjected BALB/cJ mice were assayed for both B-tropic and N-tropic MuLV. B-tropic and N-tropic MuLV were detected earlier (12 and 20 wk, respectively) in a greater proportion of mice and in higher titers compared to the controls, indicating that GVHR accelerated the induction of both viruses in CAF₁ mice. Secondly, GVHR preferentially enhanced the replication of B-tropic MuLV; titers of B-tropic MuLV were consist-

ently $10 \times$ those of N-tropic MuLV. MuLV were detected somewhat earlier (20 wk) in BALB/cJ control mice. Viral expression was biphasic in GVHR-CAF₁ mice showing large titers of virus detected at 12-20 wk and 40-44 wk. The dividing cells which are available in the GVHR animals may enable endogenous MuLV to pass through several cell generations leading to earlier and higher titers of infectious virus. (16 refs.)

77-0915 Polymorphism of the Major Envelope Glycoprotein (gp70) of Murine C-Type Viruses: Virion Associated and Differentiation Antigens Encoded by a Multi-gene Family. (Eng.) Elder, J. H. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Jensen, F. C.; Bryant, M. L.; Lerner, R. A. *Nature* 267(5606): 23-28; 1977.

The primary structure of 27 different virion-associated gp70 molecules and of the gp70's isolated from the sera and seminal fluid of nine different strains of mice was compared. Based on the tyrosine-containing tryptic peptides of these gp70's, the C-type viruses of murine origin could be divided into several groups with different degrees of relatedness. Polymorphism existed within each of these groups. Compared to viruses recently isolated from inbred or wild mouse populations, the gp70's of the laboratory-derived murine viruses (Friend, Rauscher, Moloney) varied extensively in structure. The structure of the gp70 found free in the serum of all mice tested was relatively conserved. It seemed to be the product of the same or a similar xenotropic virus gene regardless of how many other proviruses the mouse may harbor. The provirus coding for the serum protein was distinct from that coding for the genital tract gp70, indicating that unique proviruses are expressed at different anatomical sites. These findings confirm the suspicion that C-type viral tropism is largely determined by the nature of the gp70 product expressed. (27 refs.)

77-0916 Intracisternal A and Bar-Shaped Particles in Murine Neuroblastoma C 1300. (Eng.) Hayano, M. (Dept. Neurology and Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455) Sung, J. H.; Song, C. W.; Clement, J. J. *J Neuropathol Exp Neurol* 36(1): 62-73; 1977.

Transplantable murine neuroblastoma C1300 was studied ultrastructurally at varying time intervals either without or following irradiation. Eleven of 33 male A/J mice, which received sc transplants of small fragments of the tumor into their flanks, served as controls. The implanted tumors were examined 2-40 days after transplantation without irradiation. The remaining 22 animals received local radiation (17 received 2,000 rads and 5, 4,000 rads in a single dose) to the transplanted tumor 10-13 days after transplantation. The tumors were examined 2 hr-14 days after irradiation. Starting

at 1-2 days after irradiation, the uniformly small tumor cells became progressively enlarged, multinucleated, and degenerated. At 5-7 days, the uni- and multinucleated giant cells predominated over the small tumor cells; the giant cells progressively disappeared thereafter, and the small tumor cells predominated over the giant cells at 10-14 days. The giant cells contained abundant subcellular organelles, and the irradiated tumor cells apparently continued to produce the organelles until they degenerated. Two types of cytoplasmic particles, intracisternal A and bar-shaped, were observed in the tumor cells. The intracisternal A particles occurred in almost all nonirradiated tumor cells, but their number varied considerably from cell to cell. They were observed less frequently in the radiation-induced giant cells, probably due to a dilution effect rather than an actual numerical decrease. The bar-shaped particles, previously unreported in a neuroblastoma, were 23 nanometers in diameter, variable in length, and occasionally tubular. They occurred only in degenerating cells, regardless of irradiation, but were encountered more frequently in irradiated tumors than in nonirradiated ones. They may represent an unknown degenerative product of cytoplasm and/or nucleus rather than virus particles, despite their morphological resemblance to certain virus particles. (36 refs.)

- 77-0917 Murine Type C Viral Envelope Glycoprotein gp 69/71 and Lupus-Like Glomerulonephritis of New Zealand Mice. An Immunoperoxidase Study.** (Eng.) Imamura, M. (Hosp. Special Surgery, 535 East 70th St., New York, NY 10021) Mellors, R. C.; Strand, M.; August, J. T. *Am J Pathol* 86(2): 375-386; 1977.

Lupus-like glomerulonephritis and murine type C viral envelope glycoprotein gp 69/71 of New Zealand mice are assessed. The immunofluorescence labeling of the cryostat sections of NZB and NZB/NZW F₁ mouse kidneys demonstrated bright granular deposition of envelope glycoprotein antigen outlining the glomerular capillary loops and the mesangia. The mesangial labeling of this protein was more prominent in the glomeruli of NZB mice than in those of NZB/NZW F₁ mice. Specific labeling was also observed at the cytoplasm of proximal tubular epithelial cells and on the cell membranes of some of the lymphoid cells infiltrated in the kidneys. Cryostat sections labeled with immunoperoxidase uniformly reproduced the same pattern of specific labeling as shown by the immunofluorescence. Reaction products in typical brown color were seen in the peripheral capillary loops and in the mesangia of NZB and NZB/NZW F₁ mouse glomeruli. The immunoperoxidase labeling appeared to reveal more precise localization of envelope antigen in the glomeruli than did immunofluorescence labeling. In addition to the intraglomerular labeling, specific labeling by immunoperoxidase was also observed at the brush border of proximal tubules and some of the infiltrating lymphoid cells. The glomerular lesions of NZB and NZB/NZW F₁ mouse kidneys observed by electron microscopy included extensive mesangial and focal subepithelial deposits of electron-dense

materials. By the diffusion localization method, there was weak to dense labeling with goat anti-gp 69/71 serum of subepithelial deposits in the peripheral capillary loops of the glomeruli. The positive labeling of the subepithelial deposits sometimes had a tendency to become weaker at the inner aspect. Cryostat kidney sections labeled by the surface localization procedure and examined by electron microscopy appeared to preserve the framework of glomerular capillary loops. Subepithelial and mesangial deposits were easily identified and were labeled by immunoperoxidase as a strongly electron-dense material. Viral envelope antigen is present in virtually all glomerular electron-dense deposits. (25 refs.)

- 77-0918 Effect of RNA on Tumor Growth in Mouse Lines with and Without Tumor Virus.** (Rus.) Tomsons, V. P. (Inst. Cytology and Genetics, Siberian Branch, Acad. Sciences USSR, Novosibirsk, USSR) Verevkin, K. N.; Matienko, N. A. *Dokl Akad Nauk SSSR* 232(1): 217-220; 1977.

The effect of exogenous RNA and oligoribonucleotides (ORN) on the growth of syngeneic mammary adenocarcinoma (MA) with or without Bittner virus was studied in C3H/HE, A/HE and (C3H/HexC57BL)F₁ mice carrying Bittner virus, and in C3Hf and (C57BL × C3H/He)F₁ mice without Bittner virus. MA (0.2 ml of 20% cell suspension) was transplanted sc into 2- to 3-mo-old animals. RNA or ORN (260 nanomoles/10 g body) were injected qod for 10, 30, or days before, and/or for 1-2 mo after tumor injection. The tumors were weighed 1 day after the last injection. RNA and ORN, injected into Bittner-virus-carrying mice, inhibited the growth of Bittner-virus-containing transplanted MA; the tumor weights were 30-90% of the controls not treated with RNA and ORN. RNA and ORN either had no effect on or stimulated the growth of Bittner-virus-containing MA transplanted from C3H/He mice into mice carrying no Bittner virus. RNA and ORN did not inhibit the growth of syngeneic MA containing no Bittner virus, in mice carrying no Bittner virus. The findings indicate that exogenous RNA and ORN inhibit the growth of oncornavirus-containing syngeneic tumor in virus-carrying animals; the effect of RNA and ORN correlated with the quantity of oncornavirus in the organism and in the transplanted tumor. (11 refs.)

- 77-0919 A New Antigen Induced by Oncornavirus D in Mouse Fibroblast Culture.** (Rus.) Korosteleva, V. S. (D. I. Ivanovskii Inst. Virology USSR Acad. Medical Sciences, Moscow, USSR) Kosyakov, P. N.; Pavlyuchenkova, R. P.; Kosyakova, N. P. *Vopr Virusol* (5): 526-531 1976.

CFT and immunofluorescence were used to study oncornavirus D in continuous mouse fibroblast cultures. Inoculation of the virus into the cultures induced a new antigen which differed from those of the virus and of the original

infected cells. The antigen accumulated during cultivation of the infected cells. Oncornavirus preparation inactivated by heat or neutralized by antiviral antiserum did not inactivate the antigen. The physicochemical and immunological properties of the antigen are identical to those of the antigen present in cultures of J-96, HeLa and HEP-2 cells. (9 refs.)

920 **Detection of Components of D-Type Oncornaviruses in the Mitochondria of HEP-2 Cells.** (Rus.) Ershov, F. I. (D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, Moscow, USSR) Kara, I.; Zaitseva, V.; Posevaia, T. A.; Cherna, G.; Champor, F.; Zhdanov, A. *Vopr Virusol* (6): 696-701; 1976.

Experimental data on a virus-specific antigen and subviral particles in the mitochondria of HEP-2 cells, which produce type oncornaviruses, are presented. Approx 5×10^8 HEP-2 cells were suspended in 8 ml of 0.25 sucrose. The mitochondria were isolated with ^{32}P and the submitochondrial fraction was analyzed; the antigens were obtained from the HEP-2-cell culture. Rabbit-antiviral and anticellular sera were used. The mitochondria harbored electroopaque subviral particles (buoyant density, 1.27-1.28 g/cm³) that were isolated in the mitochondria de novo. Various methods of immunogenic analysis (complement fixation, immune precipitation and autoradiography) were used to determine the intramitochondrial localization of oncornavirus D-type protein. The authors suggest that mitochondria play a direct role in virus reproduction. (31 refs.)

921 **Melanoma Enhancement by Viral-induced Stress.** (Eng.) Riley, V. (Pacific Northwest Res. Foundation and Fred Hutchinson Cancer Res. Center, Seattle, WA) Spackman, D. *Pigm Cell* 2: 163-173; 1976.

The influence of biological stress in promoting the enhancement of tumor growth was investigated in the pigmented B-16 melanoma, a slower growing nonpigmented B-16 melanoma and the Gardner lymphosarcoma. Biological stress was induced by infecting tumor-bearing mice with a relatively benign murine agent, the lactate dehydrogenase-elevating virus (LDH-virus), by the direct administration of a synthetic steroid, dexamethasone (DMS) or by controlled anxiety-stress. The virus enhanced tumor growth and increased the percentage of lethal tumor takes following transplantation in the Gardner lymphosarcoma and the nonpigmented melanoma, but it did not affect the rapidly growing pigmented tumor. Similar effects on tumor growth were seen with DMS and the anxiety stress. All three stresses also induced a temporary increase in plasma corticosterone, followed by thymus involution and T-cell destruction. These observations indicate that experiments using mouse models for the study of immunological and neoplastic problems may be compromised by the inadvertent and unappreciated stress

that is present in mice maintained in conventional facilities and handled by the usual techniques. The results also indicate that the increase of plasma corticoids that occurs during pregnancy carries risk of neoplastic enhancement. (23 refs.)

77-0922 **RNA Tumor Virus Expression in Mouse Uterine Tissue During Pregnancy.** (Eng.) Fowler, A. K. (Viral Oncology, Div. Cancer Cause and Prevention, NCI, Frederick Cancer Res. Center, Frederick, MD 21701) Strickland, J. E.; Kouttab, N. M.; Hellman, A. *Biol Reprod* 16(3): 344-348; 1977.

Pregnancy resulted in a biphasic increase in total type C virus p30 in the uteri of NIH Swiss mice. The first, a twofold increase, occurred shortly after coitus and the second, which culminated as a tenfold increase over precoitus levels, occurred during the terminal wk of gestation. The number of budding and mature virus particles was greatest during and shortly after implantation. Electron microscopy and immunofluorescence of uterine tissue demonstrated virus within the uterine secretory epithelium. Mature particles were seen in the intercellular spaces of the endometrium, as well as budding from epithelial cells proximal to the basal lamina. Pregnancy modifies expression of type C RNA virus in the uteri of NIH Swiss mice. It seems likely that estrogen is responsible for this effect. (22 refs.)

77-0923 **Proliferation of a Rat Fibroblast Culture Chronically Infected with Oncogenic A-12 Virus.** (Rus.) Ageenko, A. I. (Lab. Virology, P. A. Gertsen Moscow Scientific Res. Inst. Oncology, Moscow, USSR) Kogan, I. I. *Vopr Onkol* 22(9): 78-79; 1976.

In a study designed to evaluate the effect of a viral infection on DNA synthesis, a culture of the rat fibroblasts was infected with oncogenic A-12 virus (10^5 units/ml) and 20-21 days later, when it was chronically infected, was reexposed to A-12 virus. Mitotic activity in the chronically infected culture was significantly higher than in the control uninfected cells ($p = 0.001$). However, repeated infection with A-12 virus did not induce DNA synthesis. (4 refs.)

77-0924 **Replication of Mouse Mammary Tumor Virus in Tissue Culture. 1. Establishment of a Mouse Mammary Tumor Cell Line, Virus Characterization, and Quantitation of Virus Production.** (Eng.) Sarkar, N. H. (Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021) Pomenti, A. A.; Dion, A. S. *Virology* 77(1): 12-30; 1977.

Certain aspects of mouse mammary tumor virus (MuMTV) morphology are discussed, along with the kinetics of virus production in the MuMT-73 cell line and the biochemical and

immunological characteristics of the tissue-culture-grown virus. Thin-section electron microscopy of the cultured cells showed the presence of budding and extracellular, mature, B-type virions. These findings were confirmed by negative staining. Immunological testing showed that a certain percentage of the cells were always positive for MuMTV antigens but that all cells were negative for murine leukemia virus antigens. Polyacrylamide gel electrophoresis of the purified virus revealed five major polypeptides, two glycopeptides with molecular wts of 55,000 and 34,000 and three non-glycopeptides with molecular wts of 28,000, 18,000, and 12,000. Using immunofluorescence, it was discovered that between 0 and 3 days after seeding, 25% of the cells were weakly positive for MuMTV antigens. Max fluorescence was attained at about day 6 and maintained until day 10. During this period of max viral antigen synthesis, only about 35% of the cells were positive. Reverse transcriptase measurements demonstrated that the amount of virus that could be collected from the tissue culture depended upon the time of harvest. Max yield occurred 4-6 days after the cells became confluent. Hydrocortisone and dexamethasone stimulated MuMTV production. (58 refs.)

- 77-0925 **The Structure of the Mouse Mammary Tumor Virus: Isolation and Characterization of the Core.** (Eng.) Teramoto, Y. A. (Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616) Cardiff, R. D.; Lund, J. K. *Virology* 77(1): 135-148; 1977.

A method was developed that reproducibly provides significant quantities of biophysically, biochemically, and morphologically identifiable mouse mammary tumor virus (MMTV) cores. Treatment of MMTV virions with nonionic detergents resulted in the release of RNA particles of 1.24-1.26 g/cm³ density. Pretreatment with 0.5% TX-100 for 15 min at 37 C prior to isopycnic centrifugation resulted in max recoveries of 40%-60% MMTV cores. These particles were morphologically identical to the internal core structure of MMTV virions and contained 60S-70S RNA and reverse transcriptase. The antigenic composition of MMTV was examined by immunodiffusion and by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The major polypeptides of the cores were p30, p28, and p14. Envelope glycoproteins could not be identified among any of the many minor polypeptides. (26 refs.)

- 77-0926 **Genetic Transmission of Mammary Tumour Virus by GR Mice.** (Eng.) van Nie, R. (Div. Genetics, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Amsterdam, Netherlands) Verstraeten, A. A.; de Moes, J. *Int J Cancer* 19(3): 383-390; 1977.

By immunodiffusion assay, milk samples of several strains of mice and of F₁ hybrids of the GR strain were investigated for the presence of mammary tumor virus (MTV) antigens.

When the exogenous MTV of the GR strain was introduced into BALB/c mice by foster-nursing, all milk samples of the first lactation period of these mice were negative. The presence of viral antigens in milk of the first lactation period was restricted to mice harboring endogenous MTV-GR. In the first backcross II population, [BALB/c × (BALB/c × GR × BALB/c, 33/51 mice, from immunodiffusion-positive mothers, had immunodiffusion-positive milk. However, only 1/71 mice, which were the progeny of immunodiffusion-negative backcross I mothers, was immunodiffusion-positive. A correlation was noted between the occurrence of both spontaneous mammary tumors before the age of 13 mo and early mammary tumors after hormone treatment and the presence of virus antigens in the milk. The early expression of virus antigens in the milk and the early appearance of mammary tumors in the GR strain seem to be controlled by the same genetic factors. (22 refs.)

- 77-0927 **Characterization of a Terminal Deoxynucleotidyl Transferase Activity in Mouse Mammary Tumor Virus.** (Eng.) Ashley, R. L. (Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA 95616) Cardiff, R. D.; Manning, J. S. *Virology* 77(1): 367-375; 1977.

Mouse mammary tumor virus (MMTV) contains a DNA polymerase that acts without template direction. This enzyme catalyzes the incorporation of deoxynucleoside monophosphates into an acid-precipitable product in the presence of a preformed initiator and is characteristic of terminal deoxynucleotidyl transferases (TdT). Optimal reaction conditions include pH of 6.85 and the use of a thymidine-containing substance and initiator. Terminal transferase activity was found to be associated with both the MMTV virions and cores. Manipulation of optimal conditions established a functional separation of RNA-dependent DNA polymerase (RDDP) and TdT. S₁ nuclease digestion revealed that most of the TdT reaction product was single-stranded. Terminal transferase does not require exogenous template instruction but endogenous poly(A) could have a template function in this reaction. (25 refs.)

- 77-0928 **Mouse Mammary Tumor Virus Production Stimulated by Hormones and Polyamines in Cells Grown in Semi-synthetic In Vitro Conditions.** (Eng.) Svec, J. (Cancer Res. Inst., Bratislava, Czechoslovakia) Links, J. *Int J Cancer* 19(2): 249-257; 1977.

Sykes' mouse mammary tumor cell line CCL-51, adapted to grow in semisynthetic medium, was studied to analyze the hormonal regulation of mouse mammary tumor virus (MMTV) genome expression. Reverse transcriptase activity was used to quantitate the virus. The cells were found to produce detectable amounts of MMTV spontaneously in the absence of any hormones. Treatment with dexamethasone resulted in a hundredfold increase in MMTV production. MMTV production increased with time of exposure and

number of subpassages. A combination of insulin and prolactin enhanced the stimulatory effect of dexamethasone, but insulin or prolactin alone had no effect on spontaneous MMTV synthesis. MMTV production was stimulated by spermidine but not by spermine or $MgCl_2$. Pretreatment of cells with 5-bromodeoxyuridine resulted in the suppression of dexamethasone-stimulated production. (29 refs.)

0929 Isolation of Feline Leukemia Virus from Clinical Specimens. (Eng.) Hinshaw, V. S. (St. Jude Children's Res. Hosp., PO Box 318, Memphis, TN 38101) *J Vet Res* 38(1): 55-57; 1977.

Specimens obtained from 28 feline leukemia virus (FeLV)-positive household cats were examined for infectious FeLV. Specimens (oral swab, urine, feces) were processed by virus-forming assay on a cloned 8C subline (A-81), a Moloney-murine sarcoma virus-transformed cat cell line. If positive, the samples were then tested in feline embryo fibroblasts (FEF) to confirm the presence of FeLV by fluorescent antibody. Low levels of FeLV were detected in 2/10 oral samples; however, 17/27 samples tested produced cytopathic effects in tissue culture that prevented FeLV detection. Three of 24 oral samples and 1/20 fecal specimens were positive for FeLV. One milk sample contained high levels of FeLV. All samples listed as positive were positive in both A-81 and FEF assays. Since the minimal infective dose of FeLV has not been determined, the excretion of any infectious virus must be considered a possible source of infection for other animals. These results support the recommended control measures to prevent contact of healthy cats with FeLV-positive cats. This caution is the only available method that might be used to reduce the frequency of this disease in cats. (12 refs.)

0930 Cell Culture Factors Influencing In Vitro Expression of Mouse Mammary Tumor Virus. (Eng.) Fine, D. L. (RNA Virus Lab., NCI Frederick Cancer Research Center, Box B, Frederick, MD 21701) Arthur, L. O.; Wang, L. J. *In Vitro* 12(10): 693-701; 1976.

Cell culture factors affecting the in vitro expression of mouse mammary tumor virus (MMTV) in the mouse adenocarcinoma cell line Mm5mt/C₁ were assessed. Replicate flasks were seeded with densities of $1, 3, \text{ or } 5 \times 10^6$ Mm5mt/C₁ cells per flask in the presence of DMEM-high glucose medium containing dexamethasone (DXM) and monitored over 4 days for the production of RNA-dependent DNA polymerase (RDDP). The other media evaluated were DMEM-low glucose, RPMI-1640, medium 199, L-15, and EMEM. Although a tenfold increase in RDDP activity was associated with DXM treatment for each seeding density, the greatest expression, either on a per-cell or per-milliliter basis, was observed in cultures seeded at 5×10^6 cells per flask. No differences in time of max expression of MMTV antigens (day post-DXM stimulation) were noted with any of the media tested. However, max expression (percent cells positive for

MMTV antigens) ranged from 70%-88%, with the highest values occurring in the EMEM-propagated cultures. Max expression of extracellular RDDP activity was observed 8 days post-DXM stimulation, and it varied with respect to the type of medium used. The highest activities were 490 and 910 picomoles/ml/hr/ 10^6 cells in RPMI-1640 and DMEM media, respectively. Between five- and tenfold higher RDDP activities were observed in DMEM-high glucose (4,500 mg glucose/liter) compared to DMEM-low glucose (1,000 mg/liter) cultures. Insulin alone had essentially no MMTV-RDDP stimulating activity. The presence of DXM resulted in a 10- to 30-fold increase in RDDP, depending on the medium used. Insulin in combination with DXM resulted in a 19- to 45-fold increase over the nontreated or insulin(alone)-treated cultures. The lack of cumulative RDDP activity at 37 C compared to 32 and 34 C suggested that MMTV activity could be unstable at 37 C. Incubation of Mm5mt/C₁ cells at 37 C resulted in higher levels of virus production, as determined by virus particle count, antigen expression, and RDDP activity. However, a reduction in RDDP activity occurred concomitantly as a result of the thermostability of the virus and/or RDDP at the higher temperature. Virus expression in continuous mammary cell cultures is thus influenced by a variety of factors, including seeding density, culture medium, and incubation temperature. (30 refs.)

77-0931 Horizontal Transmission of Feline Leukemia Virus Under Natural Conditions in a Feline Leukemia Cluster Household. (Eng.) Essex, M. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA 02115) Cotter, S. M.; Sliski, A. H.; Hardy, W. D.; Stephenson, J. R.; Aaronson, S. A.; Jarrett, O. *Int J Cancer* 19(1): 90-96; 1976.

Ten 4-mo-old cats, designated "tracers", were placed in a feline-leukemia-cluster household to determine the efficiency of horizontal transmission of feline leukemia virus (FeLV). The tracer cats were found to be negative for prior exposure to FeLV. Following placement in the leukemia cluster environment, the tracer cats were serologically monitored at 3-6 wk for 1 yr. The tests were: the detection of FeLV using fixed-cell immunofluorescence; titration of antibody to the feline oncornavirus-associated cell membrane antigen (FOCMA); titration of viable FeLV by serum neutralization, and determination of virion core protein p30, and virion glycoprotein gp70, using radioimmunoprecipitation. All of the tracer cats had evidence of horizontal infection by FeLV. Infection with FeLV occurred after 50-150 days of exposure. Seven of the 10 had virus that could be isolated from plasma; these 7 developed a terminal illness within 18 mo; (3 aplastic anemia, 3 infectious peritonitis, and 1 lymphoma). The remaining three were negative for FeLV by both virus isolation and fixed-cell immunofluorescence. These three did, however, develop high antibody titers by all four criteria and they remained healthy throughout the study. These results indicate that unprotected post-weaning cats brought into a leukemia-exposure household environment have a high risk of

becoming infected with FeLV. Furthermore, a large proportion of these cats are at risk for development of persistent viremia or FeLV-related diseases such as infectious peritonitis. (37 refs.)

- 77-0932 Retinal Neoplasia and Dysplasia. I. Induction by Feline Leukemia Virus.** (Eng.) Albert, D. M. (Howe Lab. Ophthalmology, Harvard Medical Sch., Mass. Eye and Ear Infirmary, 243, Charles St., Boston, MA 02114) Lahav, M.; Colby, E. D.; Shaddock, J. A.; Sang, D. N. *Invest Ophthalmol* 16(4): 325-337; 1977.

The dysplastic and neoplastic changes of the retina were examined by a light microscopic study when 0.1 ml (10^4 tissue culture infective dose) of Rickard's feline leukemia virus (FeLV) was injected ip into fetal kittens on day 40 of pregnancy. The same quantity of virus was also injected into the right and left eyes of new-born kittens on the day after birth. A third group, serving as controls, consisted of non-injected kittens. Regardless of the route of infection, all animals had similar distribution and severity of ocular inflammation (keratitis, peripheral anterior synechia, chamber angle infiltration, cataracts, iridocyclitis, choroiditis, retinitis, vitreitis, optic neuritis, and meningitis). Eight animals showed intraocular neoplastic cell infiltration. One animal, injected postpartum, developed an intraocular tumor of apparent retinal origin, composed of pleomorphic cells having hyperchromatic nuclei with clumping of chromatin and large nucleoli. Retinal malformation, seen in animals infected in utero and in those infected intraocularly after birth, included formation of retinal folds, tubes, and rosettes; intraretinal cellular disorganizations; and atrophy of the retina. In the developing retinas progressive disorganization and necrosis were documented, with subsequent reorganization into cell clumps and dysplastic rosette structures. Retinal pigment epithelium showed proliferation and intraretinal migration. The mature retina exhibited full thickness folds and tubes associated with infoldings of the retinal pigment epithelium. The induction of an intraocular tumor by FeLV is significant, since this is an RNA virus-induced tumor and may serve as an animal model for the study of retinoblastomas. (58 refs.)

- 77-0933 Prevention of Oncornavirus-induced Sarcomas in Cats by Treatment with Antiviral Antibodies.** (Eng.) de Noronha, F. (Dept. Veterinary Pathology, New York Veterinary Medicine, Cornell Univ., Ithaca, NY 14850) Baggs, R.; Schafer, W.; Bolognesi, D. P. *Nature* 267(5606): 54-56; 1977.

The effects of antibody therapy on feline sarcoma virus (FeSV) infections in cats were studied using goat antiserum to feline leukemia virus (FeLV) and goat antiserum to Friend murine leukemia virus (F-MuLV). Whole globulins and immunoglobulin G (IgG) from both sera were also used. Three-week-old kittens were infected sc with cell-free FeSV tumor

extract. Six or 12 days later, whole serum, globulins, or IgG were administered once ip followed by seven sc injections over a 16-day period. All 11 control animals died after development of progressive sarcomas. Of the two antibody treatments used, the outcome with FeLV serum globulins was more effective (none of the 8 kittens tested died from tumor). Some protection against FeSV tumor development was also achieved with the MuLV gp71 IgG (2/5 kittens survived). In some cases, animals protected by the antibody treatment developed sizeable tumors at the site of virus inoculation. However, they subsequently regressed. Scar formation at the site of FeSV inoculation was observed in several recovered cats. The cases in which the tumor was detectable by palpation during antibody treatment (and then regressed) suggest that a direct interaction between the heterologous antibody and the growing tumor may occur. (8 refs.)

- 77-0934 Passive Immunity to Feline Leukemia: Evaluation of Immunity from Dams Naturally Infected and Experimentally Vaccinated.** (Eng.) Hoover, E. A. (Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Ohio State Univ., Columbus, OH 43210) Schaller, J. P.; Mathews, L. E.; Olsen, R. G. *Infect Immun* 16(1): 54-59; 1977.

A UV-inactivated feline leukemia virus (FeLV) vaccine was tested for its ability to induce humoral immunity in pregnant cats and thereby protect the kittens born to these cats from challenge with virulent FeLV. Ten pregnant cats were immunized by three to five weekly intramuscular injections of the inactivated FeLV. Neither virus-neutralizing (VN) nor feline oncornavirus-associated cell membrane antigen (FOCMA) antibody was detectable in the dams or in the 19 kittens born to these cats. When these kittens were challenged with FeLV at 2 wk of age, 18/19 developed persistent viremia and FeLV-related disease. Two cats exposed to virulent FeLV developed VN and FOCMA antibody titers and transferred protective levels of VN and FOCMA antibody to their offspring. Surviving kittens acquired 25%-100% of the maternal VN and FOCMA titers by 3 days of age, but the titers underwent linear decay to undetectable levels by 2-3 mo of age. FOCMA antibody in dams and kittens was identified as monoglobulin G. (27 refs.)

- 77-0935 Elevation of a Threonine Phospholipid in Polyoma Virus Transformed Hamster Embryo Fibroblasts.** (Eng.) Mark-Malchoff, D. (Univ. of Rochester Sch. Medicine, Dept. Biochemistry, Rochester, NY) Marinetti, G. V.; Hare, J. D.; Meisler, H. *Biochem Biophys Res Commun* 75(3): 589-597; 1977.

A new type of lipid alteration was found in hamster embryo fibroblasts after transformation by polyoma virus in vitro. Compared to normal fibroblasts, the transformed fibroblasts showed a decrease in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) and a marked increase in a th

phospholipid (PT) provisionally identified as phosphatidylthreonine. PE content, in nanomoles/ 10^6 cells, was 4 in normal and 11.8 in transformed cells; PT was 9.5 and 11.8, respectively; and PC 21.6 and 13.2 nanomoles, respectively. When cells reacted with labeled fluorodinitrobenzene (FDNB) or trinitrobenzenesulfonate (TNBS) a greater proportion of the PE reacted in the transformed cells (88 and 89%, respectively) than in the normal cells (64 and 11.8%, respectively). Phosphatidylserine and PT in transformed cells reacted with FDNB to a greater extent than that in normal cells. Neither PT nor phosphatidylserine of either type reacted with TNBS. (38 refs.)

77-0936 Induction of the Release of Viral Particles from Greene Hamster Melanoma Cells by Thymidine. (Eng.) Reid, T. W. (Yale Univ. Sch. Medicine, New Haven, CN) Russell, P.; Albert, D. M. *Pigm Cell* 2: 22-30; 1976.

The characteristics of the virus particles induced from Greene hamster melanoma cells in tissue culture by treatment with low concentrations (10^{-5} M) of thymidine were investigated and compared with other known C-type particles released from Balb/3T3 mouse cells. A comparison was also made with virus particles released from the same cells by bromodeoxyuridine (BUdR) treatment. The amount of virus particles quantitated by the viral reverse transcriptase (RT) assay. The particles released by the Greene hamster melanoma cells were very similar to the C-type particles released from mouse cells. They banded at a density of 1.14-1.16 g/ml, which corresponds to the banding density of characteristic RNA tumor virus particles. The particles also contained RT activity with characteristics similar to the RT activity of known mouse cell type particles and to the RT released by BUdR treatment of the Greene hamster melanoma cells. (12 refs.)

77-0937 Evidence for an Inhibitor of Herpes Simplex Virus in Transformed Hamster Cells. (Eng.) Miller, E. W. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Coll. Medicine, Hershey, PA 17033) *Proc Soc Exp Biol* 154(2): 168-170; 1977.

A soluble inhibitor from type 2 herpes simplex virus (HSV-2)-transformed cells, which suppresses viral replication in permissive cells, was characterized. Confluent monolayers of normal hamster embryo fibroblast (HEF) cells were treated simultaneously with 10^2 plaque-forming units (PFU) of HSV-1 and HSV-2. HEF cell extracts did not reduce the number of plaques relative to controls when they were added simultaneously with virus seeding. Extracts of HEF cells transformed by HSV-2 reduced the plaque number of both HSV-1 and HSV-2 to 40% of controls. Plaque reduction also occurred in HEF cells pretreated with HSV-2 extract for 24 hr

prior to infection. Since the extracts were removed before infection, plaque reduction is not caused by inactivating extracellular virus. The transformed cell extracts also suppressed HSV replication. The inhibitory activity of these extracts was lost when they were heated to 56 C; treatment at 37 C was without effect. The results indicated that the inhibition is not due to interferon, since interferon is heat-stable at 56 C. The inhibitor is probably intracellular, since the extract can be washed from the cells prior to infection without inhibition being affected. Since the inhibitor works within the infected or transformed cell to prevent virus production, its function might be regulatory of the viral genome. (7 refs.)

77-0938 Transformation of Rabbit Kidney by BKV(MM) Human Papovavirus. (Eng.) Mason, D. H. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Dept. Health, Education, Welfare, Bethesda, MD 20014) Takemoto, K. K. *Int J Cancer* 19(3): 391-395; 1977.

The transformation of primary rabbit kidney cells by BKV(MM), a papovavirus isolated from the urine of a child with the Wiskott-Aldrich syndrome, is reported. Approx 7-8 wk after initial exposure of the cells to the virus, several colonies of small, round, epithelioid cells appeared. Upon further subculture, these cells became predominant in infected cultures; multinucleated giant cells were also noted. The transformed cells contained no antigen that reacted with simian virus 40 U-antiserum, but they did contain BK T-antigen. On fluorescent antibody staining, the cells were positive for T antigen. The transformed cells supported the growth of rabbit kidney vacuolating virus, and they were used to quantitate the virus by plaque formation under an agar overlay. BKV(MM) was not rescued from transformed cells by chemical induction or cell fusion methods, and the transformed cells were unable to produce tumors in nude mice. The apparent difference in the transforming efficiency of BKV(MM), compared to the original BKV isolate, may be biologically significant. (16 refs.)

77-0939 Immunological Cross-Reactions of the Major Internal Protein Component from "Slow" Viruses of Sheep. (Eng.) Weiss, M. J. (Inst. Cancer Res., 701 W. 168th St., New York, NY 10032) Zeelon, E. P.; Sweet, R. W.; Harter, D. H.; Spiegelman, S. *Virology* 76(2): 851-854; 1977.

The major p27 polypeptides of the sheep "slow" viruses, visna (VV), maedi, and progressive pneumonia, were compared by radioimmunoassay. The major protein component of VV, p27, was purified. The immunologic relatedness among these viral proteins was determined from the competition of homologous- and heterologous-disrupted virions with iodinated visna virus p27 for visna antisera. The p27 antigens

of VV and maedi virus were indistinguishable from each other and were partially related to p27 of progressive pneumonia virus. It appears that the p27 components of VV and maedi virus are identical. (16 refs.)

- 77-0940 **Bovine Leukemia Virus: An Exogenous RNA Oncogenic Virus?** (Eng.) Kettmann, R. (Department de Biologie Moléculaire, Université Libre de Bruxelles, Belgium) Portetelle, D.; Mammerich, M.; Cleuter, Y.; Dekégel, D.; Galoux, M.; Ghysdael, J.; Burny, A.; Chantrenne, H. *Haematol Bluttransfus* 19: 375-389; 1976.

Bovine leukemia virus (BLV) was investigated in terms of its biochemical properties and relationship to other known type C viruses. BLV particles released from short term cultures of bovine leukemic lymphocytes were used as a source of template primer and reverse transcriptase in an RNA dependent DNA synthesis reaction. Analysis of the reaction by a simultaneous detection technique revealed 11 fractions which represented the region where 60-70S viral RNA-³H DNA copy (cDNA) complexes sediment. The presence of these complexes was a strong indication that BLV contains a high molecular wt RNA and reverse transcriptase characteristic of RNA oncogenic viruses. The density of the BLV particles averaged 1.155 g/ml in sucrose soln. Molecular hybridizations between BLV-³H cDNA and several viral RNAs indicated that BLV is not related to Mason-Pfizer monkey virus, simian sarcoma associated virus, feline leukemia virus, or avian myeloblastosis virus. However, Rauscher leukemia virus showed a slight but reproducible (3-8%) relatedness to BLV. A high preference of BLV reverse transcriptase for the divalent cation magnesium suggested that BLV might be an atypical mammalian leukemogenic type C virus. Hybridization studies using BLV-³H cDNA as a probe suggested that the DNA of BLV infected cells contains viral sequences that cannot be detected in normal bovine DNA. Thus, bovine leukemia appears to be an infectious disease on biochemical as well as on epidemiological grounds. (52 refs.)

- 77-0941 **Bovine Lymphosarcoma: Development of a Radioimmunologic Technique for Detection of the Etiologic Agent.** (Eng.) Devare, S. C (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014) Stephenson, J. R.; Sarma, P. S.; Aaronson, S. A.; Chander, S. *Science* 194(4272): 1428-1430; 1976.

A specific and sensitive radioimmunoassay is described for the major structural protein of an oncornavirus etiologically associated with bovine lymphosarcoma. The bovine leukemia virus (BLV) was obtained from tissue culture fluids of chronically infected fetal lamb spleen cells and was concentrated 1,000-fold by centrifugation in a sucrose density gradient. The major structural protein of BLV, p24, was isolated by phosphocellulose column chromatography. Goat antiserum prepared against detergent-disrupted BLV precipitated the ¹²⁵I-

labeled BLV p24 probe to the 50% level at a titer of over 1:10,000, and to a final extent of greater than 90% at a higher serum concentration. That BLV-infected but not uninfected bovine or fetal lamb cells competed in this reaction showed that the ¹²⁵I-labeled protein was specific for BLV. Sera obtained from 25 (out of 25) cases of adult bovine lymphosarcoma were serologically reactive against BLV p24. Approximately 50% of these sera showed titers greater than 1:10,000, and in several instances titers as high as 1:50,000 were measured. In the high leukosis herd, sera from 17 (out of 20) cattle including 3 animals demonstrating evidence of clinical disease, showed serologic reactivity against BLV by radioimmunoassay. Antiserum titers varied from 1:40 to 1:16,000. Sera from leukemic cattle contained antibody to BLV p24. Sera from almost 400 clinically normal cattle were examined for exposure to BLV. These included samples from randomly selected dairy cattle from several different herds in Ontario, Canada, and Maryland. The results indicated that 10% of the animals tested exhibited antibody to BLV. Titers as high as 1:12,000 were observed. The frequency of infection with BLV in cattle may be much higher than is clinically recognized. The radioimmunoassay for BLV should be useful in future epidemiologic studies in which the magnitude of BLV infection in cattle must be ascertained. (22 refs.)

- 77-0942 **Early Syncytium Formation Induced by Bovine Leukemia Virus in Mixed Cultures.** (Eng.) Gengen, K. (Groupe d'Etude de la Leucose Bovine, Ecole Nationale Vétérinaire, 94701, Alfort, France) Pinelli, C.; Guillemin, B.; Levy, D.; Parodi, A. L. *Biomedicine* 27(2): 49-53; 1977.

Early syncytium formation induced in mixed cultures by bovine leukemia virus (BLV) is discussed. BLV-producing fetal lamb kidney cells (FLK-BLV) cocultured with mouse sarcoma virus-infected cat cell line CC81 had numerous multinucleated giant cells when stained by the May-Grunewald Giemsa technique, as did feline embryo cells cocultured with FLK-BLV. Both BLV-infected ovine and bat cells were able to induce syncytia formation with CC81 cells. No syncytium formation occurred when CC81 cells were cocultured with 12 uninfected cell lines or with cell-free BLV preparations. Incubation of FLK-BLV cells with antibody containing sera from leukemia-infected cows reduced syncytium formation. Early syncytium induction in mixed cultures using CC81 cells as indicator cells is specifically dependent on the presence of BLV and/or viral or cellular antigens associated with BLV expression. The detection of BLV infection in cattle is suggested as an application of these observations. (10 refs.)

- 77-0943 **Herpesvirus Transcription: Altered Regulation Induced by FUDR.** (Eng.) Cohen, J. C. (Department of Microbiology, Univ. Mississippi, Medical Center, Jackson, MS 39216) Perdue, M. L.; Randall, C. C.; O'Callaghan, J. *Virology* 76(2): 621-633; 1977.

scription of the genome of equine herpesvirus type 1 (V-1) in the presence of 5-fluoro-2-deoxyuridine (FUDR) is the time course of specific viral transcript production. It can be demonstrated both by competitive hybridization and by data from Scatchard analyses of saturation hybridization. Inhibition of viral DNA synthesis blocks transcription of a portion of the viral genome and alters the relative abundance of the RNA classes. Competitive hybridization studies are expressed by the double-reciprocal plot method in which the reciprocal of the percentage competition is plotted against the reciprocal of the amount of competing RNA. The Scatchard method involves the analysis of a mixture of two RNA populations, each consisting of two RNA size classes. The study shows the importance of the regulation of viral DNA synthesis in the regulation and promotion of herpesvirus transcription. (30 refs.)

944 **Cytotoxic Interactions of Virus Specific Effector Cells with Virus Infected Targets of Different Cell Type.** (Eng.) Koszinowski, U. (Tumour Immunology Zoology Dept., Univ. Coll., Gower St., London WC1E 6BT, England) Ertl, H. *J Immunogenet* 4(2): 107-114; 1977.

SV-infected mice were inoculated ip with either vaccinia, lymphocytic choriomeningitis, or Sendai virus (SV), and their spleen cells were harvested 7 days later. Cytolytic activity was tested on macrophage targets infected with the sensitizing virus. Lymphocyte activity was restricted to the virus to which the lymphocyte donors were sensitized, reflecting the virus specificity of the new determinant induced by viral infection on the cell surface. SV-specific sensitized cells from DBA/2 (H-2k), DBA/2 (H-2b), and C57Bl/6 (H-2b) mice were tested with normal and SV-infected macrophages bearing one of the three haplotypes; the effector cells killed only SV-infected target cells. When SV-infected L-929 cells (H-2k) mastocytoma tumor cells P-815 (H-2d), Methy-A-23 (H-2d), and EL-4 (H-2d) were used as target cells, cross killing of allogeneic H-2-incompatible target cells was observed. SV-specific cytolytic T lymphocytes (CTL) failed to kill SV-infected Meth-A cells, but after vaccinia virus infection these target cells were susceptible to lysis by vaccinia virus-specific CTL. This suggests that vaccinia virus may act on membrane properties by rearranging surface structures or removing components interfering with T-cell mediated lysis. (25 refs.)

945 **Transformation-Induced Alterations in Adhesion. Binding of Pre-formed Cell Aggregates to Extracellular Matrix Layers.** (Eng.) Cassiman, J. J. (Centrum Voor Menstruele Erfelykheid, Minderbroedersstraat, 12, 300 Leuven, Belgium) *Exp Cell Res* 103(2): 311-320; 1976.

Transformation-induced changes in adhesion are assessed. Formation of intercellular adhesions by mouse 3T3 cells and their simian virus (SV)40-transformed derivatives is determined by measuring the binding of pre-formed aggregates of these cells to a plastic substratum or to cell

layers. Binding of 3T3 aggregates increased immediately after initiation of the reaction, whereas binding of 3T3SV aggregates showed a brief lag. After a 30-min reaction with medium-treated plastic, the bound aggregates of both 3T3 and 3T3SV cells demonstrated many irregular projections, consisting of either large cell processes or whole cells. The 3T3SV aggregates showed projections when bound to either cell type, but the 3T3 aggregates bound to cell layers showed very few projections, which were smaller than those of 3T3 aggregates. The influence of temperature on aggregate binding was determined. Aggregate binding was generally minimal below 10°C. With increasing temperature, aggregate binding increased. The binding of 3T3SV aggregates to 3T3 layers was essentially independent of temperatures below 30°C. The transitional temperature on plastic for the binding of 3T3 aggregates was lower than for 3T3SV aggregates. Either cell layers or aggregates were treated with 0.05% glutaraldehyde for 15 min followed by extensive washing with assay medium to react any residual aldehydic groups. 3T3SV cells were significantly more resistant to inhibition of binding than 3T3 cells. The degree of inhibition with treated 3T3SV aggregates was similar on all substrata, but with treated 3T3 aggregates, the degree of inhibition varied with the substratum. Treated 3T3 aggregates bound substantially less well to 3T3SV layers than to homologous layers and not at all to plastic. The ability of neoplastic cells to invade normal tissues may be due, in part, to abnormalities in adhesive interactions between the normal and neoplastic cells. (17 refs.)

77-0946 **Genome Structures of Reiteration Mutants of Simian Virus 40.** (Eng.) Davoli, D. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA 02115) Ganem, D.; Nussbaum, A. L.; Fareed, G. C.; Howley, P. M.; Khoury, G.; Martin, M. A. *Virology* 77(1): 110-124; 1977.

Electron microscope heteroduplex analysis, DNA-DNA reassociation tests, and endonuclease cleavage patterns were used to study the structure of reiteration mutant genomes in simian virus 40 (SV40). Intracellular viral DNA was selectively extracted, and the circular, covalently closed, superhelical SV40 DNA duplex (DNA I) was purified by ethidium bromide-caesium chloride isopycnic centrifugation. The monomer fragments were purified from specific reiteration mutants by cleavage with either endo R.EcoRI or R.HindII plus III. Monomer fragments a_1 and a_1' appeared early during serial undiluted passages of two independent SV40 stocks and were found to contain similar regions of the SV40 genome. A structural distinction between the two fragments was inversion of the origin region of fragment a_1 with respect to the polarity of the late gene region sequences. Another reiteration mutant was able to reassociate five times faster than SV40 DNA. This indicated a genome with approximately 20% of the complexity of SV40 DNA. Reassociation kinetic studies demonstrated that the host sequences contained in this monomer segment are reiterated 10-20 times in each diploid genome of an African green monkey kidney cell. The origin

for SV40 DNA replication was preserved and amplified in all of the reiteration mutants studied. (49 refs.)

- 77-0947 In Vitro Synthesis of Simian Virus 40 DNA. I. Synthesis by a Soluble Extract from Infected CV₁ Cells.** (Eng.) Girard, M. (Unite de Physiologie des Virus, Institut de Recherches Scientifiques sur le Cancer, C.N.R.S., B.P. n 8, 94800 Villejuif, France) Marty, L.; Cajean, C.; Suarez, F. *Biochimie* 58(9): 1101-1111; 1976.

In an investigation of the in vitro synthesis of simian virus (SV)40 DNA, the synthesis by a soluble extract from infected CV₁ cells is assessed. Cells infected with SV40 were fractionated into a nuclear and cytoplasmic fraction, and the 100,000 x gravity supernatants from each were tested for their in vitro DNA polymerase activity after concentration by ammonium sulfate precipitation. Two tests were carried out with either activated calf thymus DNA or SV40 DNA component I as template. Both the nuclear and cytoplasmic fractions displayed significant DNA polymerase activity when assayed with calf thymus DNA. However, only the cytoplasmic fraction demonstrated noticeable activity when assayed with SV40 DNA component I molecules. After incubation with the cytoplasmic fraction in the presence of ATP, the sedimentation pattern of the ³²P-labeled template DNA was shifted at neutral pH from a homogeneous 21S sedimentation constant peak to a heterogeneous peak at approx 18S. At alkaline pH, only one-third of the molecules still sedimented at 53S as a DNA component I marker, while the remainder sedimented at 16-18S as DNA component II molecules. In the presence of ATP, one-third of the template DNA molecules were converted into relaxed circular DNA molecules and two-thirds into nicked (component II) DNA molecules. The incorporation of label into DNA component II molecules reached a plateau after about 2 hr, and had no significant lag. In contrast, the incorporation of label into DNA component I molecules was linear for up to 5 hr (32°C) and demonstrated an initial lag of approx 15 min. It is suggested that the activity of the cytoplasmic system is mostly that of a repair-like process involving the breakdown and resynthesis of template DNA molecules but not net synthesis of DNA. (36 refs.)

- 77-0948 In Vitro Synthesis of Simian Virus 40 DNA. II. Evidence for a Repair Mechanism.** (Eng.) Marty, L. (Unite de Physiologie des Virus, Institut de Recherches Scientifiques sur le Cancer, B.P. n 8, 94800 Villejuif, France) Cajean, C.; Suarez, F.; Girard, M. *Biochimie* 58(9): 1113-1122; 1976.

In a study of the in vitro synthesis of simian virus (SV)40 DNA, evidence for a repair mechanism is presented. Density labeling of DNA by 5-bromodeoxyuridine (BrdU) was utilized to characterize the material synthesized by cytoplasmic extracts of SV40 infected cells incubated in the presence of

SV40 DNA component I molecules. The cytoplasmic fraction was incubated in an assay using ¹⁴C-BrdU labeled SV40 DNA component I as template. Synthesis of DNA was monitored by the incorporation of ³H-thymidine triphosphate and ³H-guanosine monophosphate. The majority of the in vitro ³H-labeled DNA sedimented at 16S or more in a pattern indistinguishable from that of the original ¹⁴C-labeled template molecules. In vitro labeling of SV40 DNA with the cytoplasmic extracts resulted essentially from a random incorporation of nucleosides into preexisting strands. The incorporation of deoxyribonucleotides by the cytoplasmic extract was due to random insertion of deoxyribonucleotide residues into both strands of the template DNA molecule and not to the actual replication of the template. The DNA product labeled in vitro by the cytoplasmic system was relaxed component I molecules. The use of viral chromatin in lieu of viral DNA did not impart to the cytoplasmic extract the ability to replicate viral DNA. No difference was detected in the nature of the DNA made in vitro by extracts from infected or uninfected cells, except that the infected cell extract was somewhat more active at making component I DNA molecules than the uninfected cell extract. The utilization of DNA complexed with histones did not give viral specificity. It is proposed that the cytoplasmic extract can only support the repair synthesis of added viral DNA. (31 refs.)

- 77-0949 Specific Interaction of T-Antigen with Simian Virus 40 DNA (Meeting Abstract).** (Eng.) Landau, T. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel) Livingston, D. M.; Aloni, Y. *Isr J Med Sci* 12(11): 1389; 1976.

- 77-0950 Reversions to Glutamine Independence in Cells of Mammals Under the Effect of Oncogenic SV40 Virus.** (Rus.) Varshaver, N. B. (I.V. Kurchatov Inst. Atomic Energy, Moscow, USSR) Marshak, M. I.; Shapiro, N. I. *Dokl Akad Nauk SSSR* 230(3): 716-718; 1976.

An auxotrophic clone of Chinese hamster cells was infected with 128 simian virus 40 (SV40) and then harvested in glutamine-deprived medium. Exposure to the virus significantly increased the number of the colonies that were able to grow on the selective medium. This study confirms the ability of SV40 to induce reverse mutations in different loci. (3 refs.)

- 77-0951 Transcription of Simian Virus 40. VI. SV40 DNA-RNA Polymerase Complex Isolated from Productively Infected Cells Transcribed In Vitro.** (Eng.) Laub, O. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel) *Virology* 75(2): 346-351; 1976.

mian virus 40 (SV40) DNA-RNA polymerase complexes
 re isolated from BSC-1 cells productively infected with
 V40 using sarkosyl extraction. These complexes sedimented
 sucrose gradients at 23S-25S. They displayed an active en-
 genous RNA synthesis. Nascent RNA chains elongated in
 tro, but no reinitiation was detected. Hybridization to RNA
 exhaustion was used to measure the complementarity of the
 vitro elongated RNA to the early (E) and late (L) SV40
 A strands. About 5% of the RNA was complementary
 the E strand and 95% was complementary to the L strand.
 imilar hybridization with the E and L strands was also ob-
 ined with RNA extracted from cells 48 hr after infection.
 he E and L strand transcriptions were inhibited to the same
 extent by low concentrations of α -amanitin, indicating that
 both are transcribed by RNA polymerase B. These results
 support a model that emphasizes transcriptional control of
 rand selection and invokes posttranscriptional processing
 nly in the choice of specific fragments of the total transcripts
 ultimately transported to the cytoplasm. A model suggesting
 at SV40 gene expression is regulated exclusively at a post-
 ranscriptional level is precluded, as the labeled RNA used
 represents only the primary RNA transcripts and not the
 products of RNA processing. As transcription of the L strand
 largely enhanced following the onset of viral DNA replica-
 on, it is suggested that the L strand is transcribed mainly
 om a special class of replicating intermediates and that the
 strand is transcribed from nonreplicating viral DNA mole-
 cules. (35 refs.)

77-0952 **Discovery of GS-Antigen of D-Type Virus in
 Cells of Human Breast Fibroadenomas.** (Eng.)
 in, K. V. (Lab. Sarcoma-Leukemia Viruses, N. F. Gama-
 ya Inst. Epidemiology Microbiology, Acad. Medical
 sciences USSR, Moscow, USSR) *Bull Exp Biol Med* 82(10):
 1549-1551; 1976.

group-specific (gs) antigen of D-type viruses, isolated from
 continuous culture of human carcinomas and having a com-
 on gs antigen with Mason-Pfizer monkey virus, was detect-
 d in the cells of 5/7 fibroadenomas of the human breast by
 combination of immunodiffusion and immunoautoradiog-
 raphy. The results indicate that the genome of D-type viruses
 integrated with the genome of fibroadenoma cells and that
 is expressed at least as far as the level of gs-antigen synthe-
 s. The mechanism of genome derepression may be connect-
 d with the function of hormones that participate in the pa-
 togenesis of breast fibroadenoma. The gs antigen of D-type
 viruses detected here is, therefore, a mark of genome expres-
 on of these viruses, which are integrated into the fi-
 roadenoma cells. (16 refs.)

77-0953 **Oncornavirus: Isolation from a Squirrel Mon-
 key (*Saimiri sciureus*) Lung Culture.** (Eng.) He-
 erling, R. L. (Div. Microbiology and Infectious Diseases,
 outhwest Foundation Res. Education, San Antonio, TX

78284) Barker, S. T.; Kalter, S. S.; Smith, G. C.; Helmke, R.
 J. *Science* 195(4275): 289-292; 1977.

Attempts were made to isolate an endogenous virus by cocul-
 tivating lung cells (SqMLu) from a stillborn, term, male
 squirrel monkey (*Saimiri sciureus*) with a fetal canine thymus
 culture (FCf2Th), a continuous dog kidney cell culture
 (MDCK), or a diploid chimpanzee fetal lung culture
 (SFRE:CL-1). Some SqMLu cells were treated with iododeox-
 yuridine (IdU) for 4 days prior to cocultivation. DNA-
 directed DNA polymerase (RDDP) was found in cocultures
 with and without IdU treatment, but not in SqMLu, FCf2Th,
 MDCK, or SFRE:CL-1 cultures alone. The RDDP activity
 has been detectable through more than 20 passages of
 SqMLu-FCf2Th coculture, without any noticeable cytopa-
 thology, an indication of the persistent nature of the virus-cell
 interaction. The virus, detected by RDDP activity, banded
 at a density of 1.16-1.17 g/ml in a 12%-60% sucrose gradient
 and showed a marked preference for ribopolyadenylate.
 oligodeoxyribothymidylate (12-18)[poly(rA).oligo(dT)12-18]
 over polydeoxyriboadenylate oligodeoxyribothymidylate (12-
 18)[poly(dA).oligo(dT)12-18]. The squirrel monkey virus
 and Mason-Pfizer monkey virus (M-PMV) could only effective-
 ly utilize polyribocytidylate.oligodeoxyriboguanylate (12-
 18) [poly(rC).oligo(dG)12-18] in the presence of Mg^{++} but
 not Mn^{++} . These two viruses also showed a preference for
 Mg^{++} when poly(rA).oligo(dT)12-18 was used as a tem-
 plate. The simultaneous detection technique showed the pres-
 ence of a 70S RNA in the squirrel monkey virus. Although
 the squirrel monkey lung virus was similar to M-PMV in its
 morphological and biochemical properties, it is antigenically
 distinguishable from M-PMV. The virus grew in cells of hu-
 man, chimpanzee, rhesus monkey, canine, and mink origin,
 but not in cells of squirrel monkey origin. These findings
 represent the first isolation of an oncornavirus with xenotrop-
 ic properties from a New World monkey. It is proposed that
 the newly isolated virus be classified as a retravirus and given
 the designation of squirrel monkey retravirus (SMRV). (24
 refs.)

77-0954 **Differential Sensitivity of Some Functions of
 Polyoma Virus to Ultraviolet Rays. Stimulation
 of Cellular DNA Synthesis.** (Fre.) Barra, Y. (Unite de Can-
 cerologie experimentale U 119 de l'I.N.S.E.R.M., 27, boule-
 vard Lei-Roure, 13009 Marseille, France) Imbert, J.;
 Planche, J.; Meyer, G. *C R Acad Sci D (Paris)* 284(3): 255-
 258; 1977.

Macrophages from the peritoneal cavity of C3H mice were
 used to study the part of the polyoma virus genome responsi-
 ble for the stimulation of DNA synthesis. The polyoma
 viruses were irradiated with UV rays (2,537 Å) at 4°C in order
 to inactivate the genome. DNA synthesis was determined
 with the use of 3H -thymidine (2.5 μ Ci/ml). The two functions
 of the polyoma virus, infectivity and induction of DNA syn-
 thesis, were dissociable after UV irradiation. The fraction of
 the genome required for stimulation of DNA synthesis repre-
 sented 39.6% of the total genome. (21 refs.)

- 77-0955 Transcription of Polyoma Virus DNA in vitro. Localization of *Escherichia coli* RNA Polymerase Initiation Sites.** (Eng.) Lescure, B. (Dept. Molecular Biology, Institut Pasteur 25, rue du Docteur Roux, 75015 Paris, France) Oudet, P.; Chambon, P.; Yaniv, M. *J Mol Biol* 108(1): 83-97; 1976.

The transcription of polyoma virus DNA in vitro is studied. The localization of *Escherichia coli* RNA polymerase binding and initiation sites on linear or superhelical polyoma virus DNA was achieved by hybridization of short synthesis complementary RNA to polyoma DNA HpaII fragments and by electron microscopy. *E. coli* RNA polymerase was bound for 5 min at 37 C with polyoma DNA F1 or F111, poly(rI) was then added to inactivate free enzyme, and the fraction of active enzyme remaining was determined. When linear polyoma virus DNA was utilized as template, the half-life of the stable enzyme-DNA complexes was equal to 5 hr at 37 C and to 3 min at 0 C. When superhelical polyoma DNA was used as template, the half-life of the stable enzyme-DNA complexes was at least 30 hr at 37 C and 50 min at 0 C. The stability of *E. coli* RNA polymerases-DNA complexes was lower with a linear than with a supercoiled template. At low ratios of enzyme to DNA (0.5:1 to 8:1), only a few enzyme molecules were bound to the DNA. These enzyme molecules were located at specific sites on the genome. At a wt ratio of enzyme to DNA of 4:1, with an equimolar concentration of polyoma DNA F1 and F111, the av number of enzyme molecules observed on each kind of template was different. *E. coli* RNA polymerase holoenzyme exhibited higher affinity for superhelical than for linear templates. Threefold more enzyme was bound to superhelical DNA than to linear DNA with an equal ratio of enzyme to DNA. At low or moderate ratios of enzyme to DNA, specific binding sites for *E. coli* RNA polymerase were present on polyoma DNA F1. They were located at 0.06, 0.25, 0.47, 0.85, and 0.98 genome lengths from the EcoRI site. There is an increased template activity of superhelical DNA relative to linear DNA. (65 refs.)

- 77-0956 Congenital Transmission of a Papovavirus of the Stump-Tailed Macaque.** (Eng.) Shah, K. V. (Dept. Pathobiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD 21205) Rangan, S. R.; Reissig, M.; Daniel, R. W.; Beluhan, F. Z. *Science* 195(4276): 404-406; 1977.

The kidneys and other tissues of five fetuses (in the second half of gestation) of the stump-tailed macaque and the kidneys of six adults were cultured and monitored for stump-tailed macaque virus (STMV), a newly recognized papovavirus of the simian virus 40 (SV40) polyoma subgroup. Cultures were monitored weekly for cytopathic effect (CPE) and periodically for STMV-specific nuclear immunofluorescence (IF), for up to 130 days. Cultures were also screened for virions of papovavirus morphology by electron microscopy after negative staining. STMV was demonstrated in kidney

cultures from each of the fetuses and from the adult macaques. There appeared to be no relationship between the time of onset of first STMV CPE in a culture and gestational age of the fetus. STMV was not identified in cultures derived from fetal lung, skin, brain, and placenta tissues. Sera from all six adults and 3/5 fetuses were tested for the presence of IF antibodies to STMV, and all were negative. It therefore seems possible that the virus remains unexpressed throughout adult life. It is not clear whether the virus is transmitted to the fetus as an infection or by genetic inheritance. (7 refs.)

- 77-0957 Purification and Characterization of Viral RNA of a Sarcoma Virus Isolated from a Woolly Monkey.** (Eng.) Scolnick, E. M. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014) Williams, D.; Parks, W. P. *Nature* 264(5588): 809-811; 1976.

Viral RNA of a sarcoma virus isolated from a woolly monkey was purified and characterized. Each fraction of a sucrose gradient was hybridized to the complementary (c) DNA from the mouse type-C virus and to the cDNA from the woolly leukemia virus. The faster sedimenting peak hybridized well to the cDNA homologous to the mouse type-C virus, and the slower sedimenting peak hybridized to the cDNA from the woolly leukemia virus. The RNA in the slower sedimenting, high molecular wt RNA was isolated from the sucrose gradient and reverse transcribed in vitro with partially purified avian myeloblastosis virus reverse transcriptase. The cDNA prepared from the woolly leukemia virus RNA hybridized to both the woolly leukemia virus and woolly sarcoma virus RNA. At saturation, approx 50% of the sequences contained in the woolly leukemia cDNA were protected by the woolly sarcoma virus RNA. The results indicated that the woolly sarcoma virus contained only a portion of the woolly leukemia genome. The crude cDNA probe prepared from the woolly sarcoma viral RNA, which contained mostly woolly leukemia virus sequences, was also hybridized to the same viral RNAs and demonstrated slightly greater hybridization to the woolly sarcoma virus RNA than to the woolly leukemia virus RNA. The woolly src probe hybridized well to the woolly sarcoma virus RNA and not at all to the viral RNA from the woolly leukemia virus. The woolly viral src sequences were detected in cellular RNA in nonproducer rat cells transformed by the woolly sarcoma virus but not in rat cells transformed by the Schmidt-Ruppin strain of Rous sarcoma virus. Woolly sarcoma virus contains two sets of nucleic acid sequences; one set is contained in the woolly leukemia virus, and another set is specific for the woolly sarcoma virus (15 refs.)

- 77-0958 Specificities of Human Immunoglobulins Reactive with Antigens in Preparations of Several Mammalian Type-C Viruses.** (Eng.) Snyder, H. W. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Pincus, T.; Fleissner, E. *Virology* 75(1): 60-73; 1976.

human sera from normal volunteers and from patients with neoplastic disease were tested for precipitating reactivity against several RNA type-C viruses with a radioimmuno-precipitation (RIP) assay. Intact simian sarcoma virus-simian sarcoma-associated virus (SSV-SSAV), feline leukemia virus (FeLV-AB), Rauscher-murine leukemia virus (R-MuLV), and Rous-associated virus (RAV-2) were labeled with ³H. Human sera showed significant titers with the SSV-SSAV, FeLV-AB and R-MuLV viruses, but not with RAV-2 of avian origin. Titrations of normal sera with SSV-SSAV indicated that these titers are at least partially due to IgG (immunoglobulin G) antibody. Tissue culture cells producing SSV-SSAV and cells producing SSAV removed 50% of antiviral activity from human serum; normal chick-embryo fibroblasts, normal rat kidney (NRK) cells, and SSV or KiMSV (Kirsten-murine sarcoma virus)-transformed nonproducer NRK cells did not. A 70,000-dalton fraction from SSV-SSAV completely absorbed reactivity. Sera of patients with neoplasms or autoimmune diseases showed marked differences in RIP titers from those of normal individuals. (53 refs.)

77-0959 Interspecies Transfer of RNA Tumor Virus Genes: Implications for the Search for "Human" Type C Viruses. (Eng.) Todaro, G. J.; Benveniste, R.; Sherr, C. J. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. pp. 369-384; 1976.

The mode of genetic transmission and the properties of endogenous C-type virogenes are discussed. These virogenes are segments of gene sequences that are an integral part of the host species' chromosomal DNA and code for production of C-type viruses. The virogenes of a particular animal species are normally repressed, but they can be activated by a variety of genetic and hormonal factors and by radiation, chemical carcinogens, and infecting viruses. C-type virogenes unique among all known cellular genes can give rise to infectious C-type virus particles. Only within the last 2 yr have endogenous C-type viruses from primates been successfully propagated. Hybridization studies using a DNA copy of baboon virus RNA were used to detect C-type viral nucleic acid sequences in primate cellular DNA. Sequences related to the baboon C-type virus were found in man, higher apes, and all Old World monkeys. Extensive attempts to isolate endogenous genetically transmitted baboon C-type viruses of many of the primate genera, including man, failed, except within a few species of baboon. Gibbon ape leukemia virus (GALV) and simian sarcoma virus-simian sarcoma associated virus (SSV-SSAV) spread under natural conditions, and they induce tumors when injected into other primates. C-type viruses also have been transferred between species that are only remotely phylogenetically related.. (29 refs.)

77-0960 Nuclear Glycogenosis and Virus-like Particles in Human Laryngeal Papilloma Cells. (Eng.)

Conforti, A. (Istituto de Patologia Generale dell'Universita, Roma, Italy) Albani, L. M.; Pizzichetta, V. *Tumori* 62(4): 357-363; 1976.

Intranuclear particles, ascribable to glycogen infiltration, were observed during ultrastructural examination of human laryngeal papilloma cells for a virological study. The biopsy specimen was obtained from a recurrent laryngeal papilloma in a 5-yr-old boy. The cytoplasm of the basal cells showed numerous mitochondria, a well-developed endoplasmic reticulum and Golgi apparatus, and numerous osmiophilic bodies. The intermediate and superficial cells showed more evident desmosomes and tonofilaments in contrast to the much less numerous mitochondria and less-developed endoplasmic reticulum and Golgi apparatus. The presence of cytoplasmic glycogen in monopartulate form was especially evident in the intermediate layer. The same cells had an enlarged nucleus, the nucleoplasm was pale and rarefied, with margination of the chromatin, and there were degrees of segregation of the nucleolar components. The enlarged nuclei in the intermediate layer contained particles that were indistinguishable from the individual monopartulate glycogen in the cytoplasm. In the nuclei of the superficial layer, a few viruslike particles composed of an internal core of varying density surrounded by a membrane coating, 400-450 Å units in size, were observed. Closely packed aggregates of membrane envelopes were also found with these structures. The identification of the intranuclear glycogen particles was verified during light microscopy by the positive reaction of some nuclear inclusions with the PAS method. The particles identified in this study are similar in appearance to those of the papovavirus group, and their prominent intranuclear localization is in agreement with the biological properties of these viruses. The finding adds supportive evidence of the role of a virus in human laryngeal papillomatosis. (22 refs.)

77-0961 Evidence for Nuclear Antigens in Cytomegalovirus-Transformed Human Cells. (Eng.) Geder, L. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033) *Nature* 265(5590): 184-186; 1977.

Nuclear antigens (NAg) in cytomegalovirus (CMV)-transformed human cells were studied. A total of 8/13 CMV-immune human sera reacted with NAg of CMV-Mj-HEL-1 cells. Depending on the immune serum utilized, 6%-80% of the cells demonstrated NAg. the reaction was intense and was located within the nuclei. There was a correlation between the CMV antibody titer of the immune sera and their reactivity with the NAg. CMV-negative human sera did not react with the nuclei of the CMV-transformed cells. All immune sera with an antibody titer > 1:64 against CMV-infected cells reacted with NAg of the transformed cells. None of the NAg-reactive sera reacted with NAg of control HEL or bladder cancer cells. The antibodies to the NAg of CMV-transformed cells sometimes appeared to develop in the convalescent phase of the infection in some cases of CMV mononucleosis. All sera that reacted with the NAg of the transformed cells

also reacted with the early (6hr) antigens of CMV-infected cells. Only 8/13 early-antigen-reactive immune sera, however, reacted with nuclear-formed cells in the anticomplement immunofluorescence test. Adsorption of serum with uninfected HEL cells did not influence the reactivity of the serum with the NA_g of CMV-transformed cells or CMV-infected HEL cells. However, when adsorbed with CMV-infected HEL cells, the immune serum lost its reactivity against the nuclei of transformed and virus-infected cells. The adsorption to the CMV-immune serum with the CMV-transformed human cells removed the reactivity with the early antigens of the CMV-infected HEL cells and decreased the reactivity with the CMV-infected cells fixed 48 hr after infection. Sera that were positive for Epstein-Barr NA_g did not react with CMV-infected or CMV-transformed cells. The NA_g of the transformed cells may be CMV-specific T antigens of CMV-transformed human cells. (4 refs.)

- 77-0962 **In Vitro Transforming Activity of EBV. I. Establishment and Properties of Two EBV Strains (M81 and M72) Produced by Immortalized *Callithrix jacchus* Lymphocytes.** (Eng.) Desgranges, C. (Unit Biological Carcinogenesis, International Agency Res. Cancer, Lyon, France) Lenoir, G.; de-The, G.; Seigneurin, J. M.; Hilgers, J.; Dubouché, P. *Biomedicine [Express]* 25(9): 349-352; 1976.

The in vitro transformation of *Callithrix jacchus* marmoset lymphocytes was studied. Lymphocytes from 10 *C. jacchus* marmosets free of antibodies to Epstein-Barr virus (EBV) were investigated for their immortalization by HKLY-28 virus. Two permanent lymphoblastoid cell lines were obtained 6 and 8 wk postinfection, respectively, and designated M72 and M81. Control cultures from uninfected lymphocytes regularly failed to develop into continuous lines. As in the case of the B95 line, the M81 and M72 lines demonstrated reattachment of cells to the bottom culture flasks and the formation of large clumps of suspended cells. Isolation of either the attached or the floating cells resulted in mixed populations of adherent and suspended cells. Electron microscopy showed that the M72 and M81 lymphoblastoid cells produced large quantities of virus particles and that they had a morphology not much different from that of the HKLY-28 line. The synthesis level of the various EBV antigens in the original cell line HKLY-28 and in the M81 and M72 cell lines was determined. Both the number of physical particles per milliliter and the immortalization titers were enhanced by 1-2 logs, respectively, by passage through *C. jacchus* lymphocytes. The M81 strain, at the time of testing, had an intermediate immortalization titer between the M72 and B95.8 strains. Since then, both the proportion of viral capsid antigen-positive cells and the immortalization titer of M81 and M72 have increased to reach 10%-13% and 10⁴ median infective dose per milliliter, respectively (comparable to that of B95.8). These viruses did not induce early antigens in Raji cells. Marmoset cell lines had a low proportion of B cell characteristics, but human cell lines such as Raji and HKLY-28 had a high proportion of the same markers. A comparison

between the original HKLY-28 line and the M72 and M81 lines demonstrates that passage in the marmoset lymphocytes significantly increases viral production and transforming activity. (11 refs.)

- 77-0963 **Properties of a Baboon Lymphotropic Herpesvirus Related to Epstein-Barr Virus.** (Eng.) Falk, L. (Dept. Microbiology, Rush-Presbyterian-Saint Luke's Medical Center, Chicago, IL) Deinhardt, F.; Nonoyama, M.; Wolfe, L. G.; Bergholz, C.; Lapin, B.; Yakovleva, L.; Agrba, V.; Henle, G.; Henle, W. *Int J Cancer* 18(6): 798-1976.

The properties of a baboon lymphotropic herpesvirus related to Epstein-Barr virus (EBV) were studied. Four lymphoblastoid cell lines, N2CB-4, 26CB-1, 8CB-1 and 13CB-1, were established after baboon splenic lymphocytes were cocultivated with lethally x-irradiated marmoset or baboon lymphoblastoid cells. The baboon cells lacked E receptors, but 46% 55% of the cells possessed C3 receptors, as demonstrated by EAC rosette formation. 8CB-1 and 13CB-1 cells produced immunoglobulin M (IgM), and an occasional cell also produced IgG; 26CB-1 cells lacked any detectable Ig production. The virus-producing cells consistently contained typical herpesvirus nucleocapsids in the nuclei and often contained nucleocapsids within the cytoplasmic matrix and/or envelope nucleocapsids within membrane-bound cytoplasmic structures. To determine the similarity of viral capsid antigen (VCA) detected in baboon or human lymphoblastoid cells anti-VCA endpoint titrations were performed with representative EBV-positive human and baboon sera against 8CB-1, 13CB-1, and P3HR-1 cells. Serum anti-VCA titers were similar regardless of the cells used: 9/11 sera had identical anti-VCA titers on each cell line, and the variation in titers with the other two sera was never greater than two- to fourfold. Antibodies against VCA were detected in 18/18 Illinois baboons and in 37/44 Sukhumi baboons. Antibody titers of the Illinois baboons were slightly higher, as 9/18 had antibody titers $\geq 1:16$ whereas 15/44 Sukhumi baboons had antibody titers $\geq 1:16$. Cellular DNA from 8CB-1, 13CB-1, and 26CB-1 hybridized only partially to the DNA of P3HR-1 virus, and the reassociation kinetics showed break point at approx 1.75, indicating that the DNA of each cell line contained viral sequences approx 40% homologous to EBV DNA. The lines have now been propagated continuously for over 2 yr. (39 refs.)

- 77-0964 **Heterogeneity of Epstein-Barr Virus Originating from P3HR-1 Cells. I. Studies on EBV Induction.** (Eng.) Fresen, K. O. (Institut für klinische Virologie der Universität Erlangen-Nürnberg, Loschgestr. 7, 85 Erlangen, W. Germany) Merkt, B.; Bornkamm, G. W.; Zuckerman, H. *Int J Cancer* 19(3): 317-323; 1977.

Infection of Epstein-Barr virus (EBV)-negative human B lymphoma cells of the BJAB and Ramos lines with EBV from

HR-1 or B95-8 cells was assessed. Prior to cloning, P3HR-1 virus-converted BJAB (BJAB-HRIK) cells were cultivated for 70 wk after infection. At this time, approx 95% of cells stained EBNA by anticomplement immunofluorescence. About 40% exhibited a brilliant fluorescence pattern, but the remaining 55% demonstrated faint granular staining. Brilliantly stained Epstein-Barr nuclear antigen (EBNA)-expressing B95-8 virus-converted BJAB and Ramos cells contained one to two genome equivalents per cell. The BJAB-HRIK(A) line contained approx 35 genome equivalents per cell. The infection of EBV-negative BJAB and Ramos cells as well as of their converted sublines with EBV from P3HR-1 resulted in significant differences in early antigen induction. Cloning of P3HR-1 virus-converted BJAB cells resulted in 20 clones. There are at least two populations of EBV molecules within P3HR-1 cells, but the reason for the labile association of P3HR-1 EBV genomes inducing the brilliant EBNA fluorescence in BJAB cells remains obscure. (18 refs.)

0965 Studies on Epstein-Barr Virus-related Antigens.

II. Biochemical Properties of Soluble Antigen

Raji Burkitt Lymphoma Cells. (Eng.) Matsuo, T. (Dept. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan) Nishi, S.; Hirai, H.; Osato, T. *Int J Cancer* 33(3): 364-370; 1977.

The biochemical properties of Epstein-Barr virus (EBV)-related soluble antigen in nonproducer Raji Burkitt lymphoma cells were assayed by indirect single radial immunodiffusion. Raji cell extracts exposed to different temperatures retained their immunodiffusion activity even after exposure to 80°C for 10 min. A test of both supernates and precipitates obtained by treatment of Raji cell extract with ammonium sulfate demonstrated that the soluble antigen was completely precipitated in a 35%-40% saturated soln. A Raji cell extract was applied to an electrofocusing column. Activity was detected as a sharp single peak, and the pH of the top of the peak was 4.8. A distinct precipitin peak was obtained when a Raji cell extract was reacted with EBV-seropositive serum at the migrating position of α -globulin. A Raji cell extract was also applied to a Sephadex G-200 column, and eluted fractions were examined by immunodiffusion and anticomplement immunofluorescence absorption. Both antigenic activities were in the same fraction as a single peak. The molecular wt of the EBV-related soluble antigen is approx 200,000-240,000 daltons. (21 refs.)

0966 Studies on an Epstein-Barr Virus-induced DNA Polymerase.

(Eng.) Miller, R. L. (Dept. Microbiology, Milton S. Eshelby Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA) Glaser, R.; Rapp, F. *Virology* 76(2): 494-502; 1977.

This study shows that cells induced to express Epstein-Barr virus (EBV) late virus functions also express a salt-stimulated

DNA polymerase activity associated with these functions. The cells chosen for this study, D98/HR-1 hybrids, were chosen because of their unique control of EBV expression. Under normal growth conditions, they provide an uninduced control and thus act like the nonproducer, lymphoblastoid Raji line, in that they repress EBV-specific early antigen (EA), virus capsid antigen (VCA), and membrane antigen (MA). However, D98/HR-1 cells grown in the presence of 5-iodo-2'-deoxyuridine (IUdR) act like producer cells and they express EA. Cells exposed to IUdR and grown in normal medium express VCA, MA, and EA. EBV-specific DNA synthesis is initiated, with subsequent appearance of virus particles. The effect of phosphonoacetic acid (PAA: 50 or 100 μ g/ml) on the expression of EBV antigens in D98/HR-1 cells treated with IUdR suggests that an EBV-specific DNA polymerase that may be induced is inhibited by PAA. Inhibition of this DNA polymerase by PAA would inhibit the synthesis of virus DNA and the expression of late antigens, such as VCA. The EBV-induced polymerase was markedly stimulated by ammonium sulfate. (24 refs.)

77-0967 The DNA of Epstein-Barr Virus Fragments Produced by Restriction Enzymes: Homologous

DNA and RNA in Lymphoblastoid Cells. (Eng.) Hayward, D.; Pritchett, R.; Orellana, T.; King, W.; Kieff, E. In: *Animal Virology. ICN-UCLA Symposia on Molecular and Cellular Biology*. Baltimore, D.; Huang, A. S.; Fox, C. F., eds. (New York: Academic Press, Inc.): Vol. 4, pp. 619-639; 1976.

The results of analysis of Epstein-Barr virus (EBV)-infected homologous DNA and RNA in continuous lymphoblastoid cell lines indicate that most of these lines contain multiple copies of EBV homologous DNA that are indistinguishable from the EBV (HR-1) DNA complex. The DSTC-4, Namalwa, and SKL cell lines contained fewer copies of EBV homologous DNA, since these lines are not permissive of viral replication and cannot have induced the early antigen associated with this process. The EBV DNA of the Namalwa and SKL cell lines contained a lower kinetic complexity than the EBV (HR-1) DNA. The extent of phenotypic expression of the EBV genome was generally correlated to the transcription of viral DNA sequence into stable RNA. RNA extracted from virus-producing HR-1 cells contains RNA sequences transcribed from at least 45% of the viral DNA, but the nonpermissive cell lines contain transcripts homologous to a smaller proportion of the EBV DNA. With the polyribosomal fraction of the Namalwa and Kurgans nonpermissive cells, only 3% of EBV HR-1 DNA is present as RNA homologs. Data on the viral RNA in extracts of the Ditzel, Raji, Namalwa, and Kurgans cells, all nonpermissive of virus replication, show that EBV homologous RNA sequences in the polyribosomal fraction come from < 30% of the total cellular viral RNA transcribed from the DNA. The DNA of EBV are suggested to consist of at least two populations of molecules in which some sequences have a common order. (33 refs.)

77-0968 Failure to Immortalize Human "Null" Cells by Epstein Barr Virus (EBV) "In Vitro". (Eng.)

Diehl, V. (Section Haematology, Medizinische Hochschule Hannover, W. Germany) Peter, H. H.; Knoop, F.; Hille, D.; Kalden, J. R. *Haematol Bluttransfus* 19: 471-473; 1976.

Failure to immortalize a subpopulation of human "Null" cells in the presence of Epstein Barr virus (EBV) is reported. Peripheral blood lymphocytes were isolated from EBV seroreactive healthy persons (13) and patients with malignant melanomas (14). F lymphocytes were depleted of iron phagocytosing macrophages and a fraction of cells adhering to plastic surface (fraction AD). The remaining nonphagocytic, nonadherent lymphocyte population (fraction FFF) was further purified, leaving a post-column fraction (FFF-C) with approximately 70% T cells and a subpopulation (30%) of "Null" cells with a low affinity for immunoglobulin G-anti-immunoglobulin G columns. Susceptibility to EBV induced blast formation was determined for 18 cultures of the FFF-C fraction and 56 cultures of the other lymphocyte fractions. The initial cell inoculum was 2×10^6 cells per culture vial in 5 ml RPMI-1640 medium supplemented with 20% fetal calf serum, penicillin, and streptomycin. EBV, derived from supernatants of B-95-8 cultures (marmoset lymphoblasts), was added to the cultures in a final concentration of 1:10. In the presence of EBV, 3/11 (27%) cultures with fraction F, 2/15 (13%) cultures with fraction FFF and 11/17 (65%) cultures with fraction AD gave rise to continuously growing cell lines. In contrast, none of 18 trials with cells of fraction FFF-C was successful (results for both control persons and melanoma patients reported together). A feeder lay of allogeneic human embryonic fibroblasts increased the survival of FFF-C lymphocytes from an original max of 10 days to a max of 2 mo, but even under these conditions EBV-induced blastoid transformation was not observed. These preliminary experiments, however, do not exclude the possibility that "Null" cell immortalization may need a higher EBV multiplicity or increased numbers of "Null" cells because of decreased EBV receptor affinity. (8 refs.)

77-0969 Tumorigenicity of Human Hematopoietic Cell Lines in Athymic Nude Mice. (Eng.) Nilsson,

K. (Wallenberg Lab., Univ. Uppsala, Box 562, S-751 22 Uppsala, Sweden) Giovanella, B. C.; Stehlin, J. S.; Klein, G. *Int J Cancer* 19(3): 337-344; 1977.

Human hematopoietic cell lines were tested for their tumorigenic potential by sc transplantation to nude mice and for their capacity to grow in semisolid medium in vitro. Nine recently established lymphoblastoid cell lines (LCL) tested failed to grow. However, 2/4 aneuploid LCL were tumorigenic. A similar, but less-pronounced, difference was found among African Burkitt's lymphoma (BL) lines. Of the new lines, 3/5 were transplantable, but 8/10 old lines demonstrated successful growth. None of the new LCL formed visible colonies. A few small clusters were observed for some lines at a frequency of < 0.1% of the cells. In contrast was the

tetraploid LCL U-255 Bm, which grew rapidly in agarose, formed visible colonies at a high cloning efficiency. Among the BL lines, two old lines were tested, and both formed clusters of cells at a high cloning efficiency. Except for diploid LCL, no clear correlation between heterotransplantability and colony formation in agarose was found. Neither the tests is a reliable criterion for the malignancy of human lymphoma myeloma, and leukemia cell lines. (82 refs.)

77-0970 Comparative Studies on EBV Antigens by Immunofluorescence and Immunoperoxidase Techniques. (Eng.) Stephens, R. (John L. Smith Memo

Cancer Res., Pfizer Incorporated, Maywood, NJ 07604) Traul, K.; Gaudreau, P.; Yeh, J.; Fisher, L.; Mayyasi, S. *Int J Cancer* 19(3): 305-316; 1977.

Three groups of Epstein-Barr virus (EBV) antigens (viral capsid, early, and membrane) were compared by electron microscopic immunoperoxidase and immunofluorescence techniques. P3HR-1- and EBV-superinfected Raji cells served as targets for labeled sera from patients with Burkitt's lymphoma, infectious mononucleosis, and nasopharyngeal carcinoma. The penetration of ^{125}I -labeled preoxidase conjugates into P3HR-1 cells was determined at 1 and 24 hr. At 1 hr there was very little penetration, but at 24 hr the positive cells were heavily labeled with grains. The percentage of positive cells correlated well with that obtained by immunofluorescence. With the membrane antigen-positive Burkitt's lymphoma and nasopharyngeal carcinoma sera, the reactions with both immunoperoxidase and immunofluorescence were patchy, indicating a random distribution of labeled antibody on the cell surface. The sera that were employed to demonstrate the virus capsid antigens by immunofluorescence produced two types of reaction. Acetone-fixed cell smears were positive for observation of early antigen by immunofluorescence. Diffuse early antigen is associated with cellular ribosomes. (22 refs.)

77-0971 Transcription of Adenovirus "Cores." (Eng.) Tate, V. (Searle Res. Labs., Lane End Rd.

High Wycombe, Bucks, England) Richards, B.; Pardon, J. *INSERM* 47: 75-82; 1975.

The transcription of free deproteinized DNA was compared with that of DNA still associated with one of the core proteins using *Escherichia coli* RNA polymerase. Cores were isolated by acetone disruption of the virus followed by precipitation of the viral cores in 0.15 M NaCl. The cores were washed repeatedly to remove contaminating coat proteins. Using the core as a template, DNA transcription was reduced 95% compared with the same amount of free DNA after 30 min incubation. The presence of core protein VII on the adenovirus DNA in the core structure may reduce transcription by blocking a number of the available binding sites. RNA chains transcribed from cores were 5-10 times smaller than those

from native DNA, indicating that elongation is being reduced in this system. For longer elongation times the profile remained the same, showing that the difference in size of the RNA chains is not the result of a reduced rate of elongation in the cores and that the profile is not due to nuclease action on the RNA chains. The findings indicate that core protein II is most likely a structural protein required to condense the DNA into a form suitable for encapsidation and, in so doing, represses transcription. (5 refs.)

77-0972 Viral DNA Synthesis In Vitro with Nuclei Isolated from Adeno-associated Virus Type 1-Infected Cells. (Eng.) Handa, H. (Inst. Medical Science, Univ. Tokyo, P.O. Takanawa, Tokyo 108, Japan) Shimojo, T. *Virology* 77(1): 424-428; 1977.

Viral DNA synthesis in vitro with nuclei isolated from adeno-associated virus type 1 (AAV1)-infected cells is described. Confluent monolayers of human embryonic kidney (HEK) cells were infected with a temperature-sensitive mutant of human adenovirus type 31 (H31tsA13) and then superinfected with AAV1. Incubation was at the nonpermissive temperature of 40 C. Electron microscope autoradiograms revealed that only AAV1-DNA was synthesized. There was no synthesis of either adenovirus or cellular DNA under these conditions. AAV1-DNA was found only in the nuclei of the superinfected cells. HEK cells superinfected with AAV1 were harvested after 16 hr incubation and their nuclei were isolated. The nuclei were examined for DNA synthesis in vitro. The results showed that DNA synthesis began to increase 6 hr after superinfection and reached a max 16 hr after superinfection. This was in agreement with AAV1-DNA synthesis in vivo. DNA synthesis was not observed in nuclei from cells infected with H31tsA13 alone. DNA-DNA hybridization studies showed that the labeled DNA synthesized in vitro was AAV1-DNA. Alkaline sucrose gradient analysis showed that DNA synthesized by coinfecting in vitro nuclei sedimented faster than marker AAV1-DNA. After treatment with papain, trypsin, and sodium dodecyl sulfate followed by extraction with phenol, this fast-sedimenting DNA shifted to the position of the marker DNA. A protein may be involved in the formation of fast-sedimenting DNA. (12 refs.)

77-0973 Mapping of Adenovirus 2 Genes by Translation of RNA Selected by Hybridization. (Eng.) Atkins, J. F. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724) Lewis, J. B.; Anderson, C. W.; Baum, P. R.; Westeland, R. F. *INSERM* 47: 293-298; 1975.

A biochemical map of adenovirus type 2 DNA was constructed by hybridizing the messenger RNA's (mRNA's) from infected cells to various fragments of the DNA obtained with restriction enzymes and translating the hybridized RNA's. Most of the proteins synthesized in adenoinfected cells at late times after infection are encoded by adeno DNA. Analysis

of the polypeptides formed with mRNA's produced at early times after infection indicated that seven specific polypeptides (72K, 52K, 45K, 19K, 15.5K, 15K, and 11K) are synthesized in vitro. Results obtained with the restriction endonuclease, Eco.RI, showed that the mRNA for the 72K DNA-binding protein is located on the map in a region of the DNA that is not necessary for transformation. The results suggest, however, that the critical parts of T antigen with respect to transformation should be located in the left-hand end of the map, a region required for establishment and maintenance of the transformed state. (20 refs.)

77-0974 Transcription of Adenovirus-2 DNA by RNA Polymerase C of HeLa Cells. (Fre.) Hossenlopp, P. (Institut de Chimie Biologique et Groupe de Recherches INSERM U. 44, Faculte de Medecine, 67085 Strasbourg Cedex, France) Wells, D.; Chambon, P. *Les Colloques de l'Institut National de la Sante et de la Recherche Medicale* 47: 43-50; 1975.

DNA-dependent RNA polymerases CI, CII, and CIII have been isolated by chromatography from adenovirus-2 (Ad2)-infected or noninfected HeLa cells. In this study, optimal conditions for the transcription of native, intact, double-stranded and denatured Ad2 DNA by these polymerases were investigated. The RNA C polymerases transcribe Ad2 DNA as readily as they do calf thymus DNA; however, the ionic strength and divalent cation requirements for transcription are drastically different. Optimum transcription of RNA occurred at a concentration of 4 mM of Mn^{++} for 2 μ g of Ad2 template, compared to 2 mM of Mn^{++} for 2 μ g of calf thymus. Native DNA from Ad2 is much more sensitive to the ionic strength of an ammonium sulfate solution than is the native DNA from calf thymus in the transcription reaction. The opposite is true for denatured DNA from Ad2 and calf thymus. Transcription of Ad2 DNA by the RNA A and B polymerases was also studied. (20 refs.)

77-0975 The Isolation and Identification of the Adenovirus Group C Tumor Antigens. (Eng.) Levinson, A. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ 08540) *Virology* 76(1): 1-11; 1977.

Two independently derived antisera (14b and Ad1-simian virus 40, SV40) from hamsters bearing distinct adenovirus (Ad) group C-induced tumors were used to immunoprecipitate and identify the tumor antigens produced in Ad-infected cells. Monkey or human cells infected with Ad5 were labeled with ^{35}S -methionine early or late after viral infection. The specific immunoprecipitates were analyzed electrophoretically to determine the molecular wt (MW) of the Ad-infected cell antigens that reacted with the antibody from the antisera. One antiserum preparation (14b) immunoprecipitated predominantly a single protein of 58,000 MW. No homologous protein was detected in uninfected cells, and normal

hamster serum failed to immunoprecipitate this antigen from infected cell extracts. The other antiserum (Ad1-SV40) specifically immunoprecipitated this 58,000 MW protein, and it also reacted with viral-specific antigens of 72,000 and 44,000 MW. All three of these viral-specific proteins were synthesized early after infection, prior to viral DNA replication. Late after viral infection, the Ad1-SV40 serum immunoprecipitated or coprecipitated a 120,000 MW protein. The 72,000 MW protein is immunologically related to the Ad single-strand-specific DNA binding protein. Some or all of the 44,000 MW protein resulted from the proteolytic breakdown of the 72,000 MW protein. The Ad5-transformed cell line 14b contained the left-hand 40% of the Ad genome. The early Ad genes carried in the 14b DNA segment are common to all Ad-transformed cell lines. It is therefore likely that the 58,000 MW protein found in Ad-infected cells is an Ad-specific tumor antigen common to all tumors and transformed cells. (25 refs.)

- 77-0976 Genetic Analysis of Adenovirus Type 2: IV. Coordinate Regulation of Polypeptides 80K, IIIa, and V.** (Eng.) Weber, J. (Departement de Microbiologie, Universite de Sherbrooke, Centre Hospitalier Universitaire, Sherbrooke, Quebec, Canada J1H 5N4) Begin, M.; Carstens, E. B. *Virology* 76(2): 709-724; 1977.

A wild-type (WT) adenovirus type 2 temperature-sensitive mutant, ts3, deficient in virion assembly was studied by gel electrophoresis and electron microscopy. The virus was grown in KB, CV₁, or HTC (SV40-induced hamster tumor cell line) cells in monolayer culture. A total of 28 virus-induced polypeptides were detected, 4 of which were precursor proteins. At the nonpermissive temperature, ts3 failed to synthesize a newly identified nonstructural polypeptide 80K. Polypeptide V was absent; it may have been replaced by an arginine rich polypeptide that was oversynthesized and migrated as a 50K band regardless of temperature. Similarly, polypeptide 55K was also oversynthesized and migrated slower than WT-55K. In addition, several polypeptides were synthesized at increased or decreased levels, compared with WT. Polypeptide IIIa was sometimes resolved into three bands (66K, 67K, 68K) in WT, while ts3-IIIa lacked the 66K and 68K components. Polypeptide 36K was found to be rich in arginine. Consistent with the idea that the processing of PVII into VII requires virion assembly, no processing of ts3-PVII was observed. By contrast, the cleavage products (VI and VIII) appeared normally, thus disputing the virion assembly requirement previously postulated for these polypeptides. Electron microscopy of ts3-infected cells revealed two previously undescribed intranuclear structures, possibly tubular forms, at the permissive temperature, and roughly spherical, core-like structures of 80-100 nm at the restrictive temperature. These results suggest that the pleiotropic effects of the ts3 mutation arrest virus assembly at the level of core-like structure. (25 refs.)

- 77-0977 Hexokinase Activity in the Soluble Nuclear Fraction and Cytoplasm of Cell Cultures Infected with Human A6 and A12 Adenoviruses.** (Eng.) Ageon, A. I. (Lab. Virology, P. A. Gertsen Oncologic Res. Inst. Moscow, USSR) Vitorgan, Y. E.; Gorozhanskaya, E. G.; Shapot, V. S. *Exp Biol Med* 81(5): 686-688; 1976.

The hexokinase activity in the soluble nuclear fraction and cytoplasm of primary trypsinized rat embryonic fibroblasts infected with human A6 and A12 adenoviruses is assessed. In the nuclear fraction of fibroblasts from rats infected with A6 adenovirus, the hexokinase activity was almost indistinguishable from normal. The av enzyme activity (6.3×10^{-4} μ moles glucose/g protein/min) in the cytoplasm likewise did not differ significantly from normal. Under the influence of A12 adenovirus, the nuclear hexokinase began to change on the third day of interaction between virus and cell. Activity of the enzyme was sharply increased in the soluble nuclear fraction on the day 18, when loci of transformation appeared in the cytoplasm. Its activity was twice as high as the av value both under normal conditions and in fibroblasts infected with A6 adenovirus. Total hexokinase activity in the cytoplasm of a fibroblast culture infected with the oncogenic virus rose sharply on the fifth day of infection with the virus. A substantial increase of activity was discovered on the day 18. On the day 24 of infection with oncogenic virus, the cytoplasmic hexokinase activity was almost 14 times higher than normal and 12 times higher than in fibroblasts infected with A6 adenovirus. Total hexokinase activity was much higher in the cytoplasm than in the nuclear fraction of the culture infected with oncogenic virus. On day 24 of interaction between A12 adenovirus and cell, when the culture was completely transformed, the total activity in the nucleus was 3.5 times greater than normal and 3.3 times greater than in fibroblasts infected with A6 adenovirus. The increase in hexokinase activity and the intensification of glycolysis in the early stages of transformation of fibroblasts under the influence of oncogenic virus can be presumed to be fundamental properties of malignant growth, possibly connected with the uncontrollability of the process of cell proliferation. (9 refs.)

- 77-0978 Purification of Adenovirus Type 12 Tumor Antigen from Transformed Hamster Cells.** (Eng.) Biron, K. K. (Dept. Microbiology, Coll. Medicine and Dentistry New Jersey, Rutgers Medical Sch., Piscataway, NJ 08854) Raska, K. *Virology* 76(2): 516-526; 1977.

Attempts to purify adenovirus 12 (Ad12) tumor (T) antigen from cell line T637 of transformed baby hamster kidney cells (BHK21) are described. The characteristic of Ad12 transformed cells of a strong binding affinity for double stranded (ds) DNA and no binding affinity for single stranded (ss) DNA was utilized in conjunction with other purification methods such as centrifugation at 15,000 g of the crude T antigen, gel filtration on Sephadex G-100, hydroxylapatite chromatography, and DEAE cellulose chromatography.

phy. The size estimate of the T antigen by gel filtration was out 80,000 daltons. During chromatography on a double-stranded DNA cellulose column, the immunoreactivity was solved into a major component eluting at pH 8 and a minor component eluting at pH 6.2. The purified preparations contained two peptides of 64,000 and 50,000 daltons, but the relationship between them and whether one or both are immunoreactive were not determined. (26 refs.)

77-0979 Mutual Stimulation of Oncornavirus and Herpes Infection In Vivo and In Vitro. (Rus.) I. F. (D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, Moscow, USSR) Shubladze, A. K.; Bolzharov, A. F.; Spynu, K. I.; Tolmacheva, V. D. *Vopr Virusol* (Moscow): 660-663; 1976.

The mutual stimulation of Rauscher leukemia virus (RLV) and herpes simplex virus (HSV, strain L₂, type 1, and strain L₂, type 2) was studied in BALB/c mice and in cell cultures (thick embryo fibroblasts, HEP-2, and J-96) by determining the virus titer in the animals, and the virus particle count in the cell cultures. The mice were infected with RLV suspension (dose 2.3 log LD₅₀, ip), and with HSV (0.1 ml suspension, ip) 36 hr later. Mice infected with only RLV or HSV served as controls. The HSV titer of the mice previously infected with RLV was higher than in the control groups. The continuous HEP-2 culture, chronically infected with RLV, was found more sensitive to the cytopathogenic effect of HSV than the control not infected with RLV. Also, the HSV titer in the liquid phase of these cultures was higher than in the thick embryo fibroblast cultures. The RLV particle count was 8.3 times higher in J-96 cell cultures chronically infected with both RLV and HSV than in cultures infected with RLV only. The findings indicate the mutual stimulation of RLV and HSV. (12 refs.)

77-0980 Structure and Function of Herpesvirus Genomes. (Eng.) Skare, J. (Dept. Therapeutic Radiology, Yale Univ., 333 Cedar St., New Haven, CT 06510) *Virology* 76(2): 581-595; 1976.

Restriction endonuclease cleavage site mapping of the herpes simplex virus type I (KOS strain) genome shows that the DNA is composed of a large segment of 80 megadaltons linked to a small segment of 16 megadaltons. The virus was grown in Vero cells. The DNA molecules fall into four distinct groups, with large and small segments joined end to end in each of the four possible orientations. In addition, the large segment shows limited heterogeneity at its ends so that more than 16 distinguishable populations of DNA molecules are possible. (22 refs.)

77-0981 The Effect of Herpes Virus Infection on mRNA in Polyoma Virus-Transformed Cells. (Eng.) Pizer, L. I. (Dept. Microbiology, Univ. Pennsylvania, Sch. of Medicine, Philadelphia, PA 19174) Beard, P. *Virology* 75(2): 477-480; 1976.

The effect of herpes simplex virus type 1 (HSV) infection on the synthesis and amount of polyoma (Py)-specific RNA was investigated in Py-transformed baby hamster kidney (Py BHK) cells by hybridization to Py DNA. Cytoplasmic RNA was isolated from uninfected Py BHK cells and from cells 5 hr after infection with HSV. Increasing quantities of these RNA were incubated with 1 nanogram of radioactive E-strand Py DNA (the DNA strand complementary to RNA present in Py-infected cells prior to viral DNA synthesis). By 5 hr after infection the amount of Py-specific RNA had fallen to 20% of that in uninfected controls, but the nucleotide sequences in the Py transcript were generally the same as before infection. RNA was labeled with ³H-uridine for 30 min at 2 and 5 hr after infection of Py BHK cells, whole-cell RNA was extracted, and the radioactivity able to hybridize to Py DNA on filters was determined. The results demonstrated that the capacity of Py BHK cells to synthesize Py RNA rapidly declines after infection with HSV and essentially stops at 5 hr. The inhibition is specific, since the decrease in RNA hybridizable to Py DNA after infection is more pronounced than the decrease in the specific activity of total RNA. These experiments indicate that HSV infection reduced both the synthesis and the steady-state level of Py messenger RNA. The lower level of Py RNA in the cytoplasm could result solely from blockage of synthesis and natural decay or from an HSV-promoted destruction of classes of RNA. (11 refs.)

77-0982 Immune Interactions with Cells Infected with Herpes Simplex Virus: Antibodies to Radioiodinated Surface Antigens. (Eng.) Glorioso, J. C. (Unit for Lab. Animal Medicine, Univ. Michigan Medical Sch., 010 Animal Res. Facility, Ann Arbor, MI 48104) *J Immunol* 118(1): 114-121; 1977.

To determine whether the herpes simplex virus (HSV) antisera contained any antibodies against BHK-21 cells, radiolabeled surface proteins of uninfected cells were reacted with rabbit antiserum to infectious HSV-1, precipitated with goat-anti-immunoglobulin G serum, and subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The only significant amount of activity detected was associated with the lighter proteins (35-40 daltons) in the lower third of the gel. At least 10 HSV-1-specific surface antigens, ranging in molecular wt from 35 x 10³ to 160 x 10³ daltons, were detected in the immune precipitates of iodinated surface antigens. Cells were tested for the appearance of surface antigens by lactoperoxidase-catalyzed radioiodination and ⁵¹Cr-release assay and the appearance of surface-adherent virions by electron microscopy. A significant number of counts was associated with radioiodinated immune precipitates as early as 2 hr postinfection. Surface antigens detectable by cytolytic antibodies in the ⁵¹Cr-release assay, on the other hand, were not observed until 4 hr postinfection. The level of extracellular infectious virus did not begin to increase until 10 hr postinfection. With electron microscopy, virions were rarely observed on cell surfaces at times earlier than 18 hr

postinfection. At 24 hr, however, large numbers of virions adherent to cell surfaces were apparent. Antigens induced by HSV-1 were similar to those induced by HSV-2. In both cases, most of the activity was associated with glycoproteins in the range 115×10^3 to 130×10^3 daltons. Results show that surface antigens capable of reacting with antibody to HSV can be labeled and distinguished from other HSV-induced antigens. (31 refs.)

77-0983 Detection of Early Antigens in Nuclei of Cells Infected with Cytomegalovirus or Herpes Simplex Virus Type 1 and 2 by Anticomplement Immunofluorescence, and Use of a Blocking Assay to Demonstrate Their Specificity. (Eng.) Giraldo, G. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Beth, E.; Hammerling, U.; Tarro, G.; Kourilsky, F. M. *Int J Cancer* 19(1): 107-116; 1977.

The specificity and cross-reactivity of early antigens (EA) of cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1), and HSV-2 were determined by anticomplement immunofluorescence (ACIF). The nuclei of 48-hr CMV, 18-hr HSV-1, 18-hr HSV-2, and cytosine arabinoside-treated fibroblasts stained positively in ACIF reactions by sera with herpes virus-determined antibodies. CMV nuclear antigens were detectable in 15% of the cells after 24 hr. Staining was originally cytoplasmic in HSV cells and predominantly nuclear after 18 hr. ACIF reactions of sera with anti-CMV-EA antibodies were routinely blocked by $F(ab')_2$ anti-CMV-EA fragments. $F(ab')_2$ from sera with low anti-EA and high anti-LA (late antigens) or from negative control sera were without effect. $F(ab')_2$ anti-HSV-EA fragments from hyperimmune sera blocked autologous sera against HSV-1-EA cells. Similar results were obtained for HSV-2. $F(ab')_2$ anti-HSV-1-LA fragments from sera with no EA but high LA reactivity could not depress the positive responses of HSV-1-EA. No cross reactions between CMV-EA, HSV-1-EA, or Epstein-Barr virus-EA were detectable. (41 refs.)

77-0984 Expression of Type-Specific Virion Structural Antigen(s) in L Cells Transformed by Herpes Simplex Virus Types 1 and 2. (Eng.) Chadha, K. C. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263) Munyon, W. H.; Zeigel, R. F. *Virology* 76(1): 433-436; 1977.

Evidence is presented indicating that L cells transformed by herpes simplex virus types 1 (HSV-1) or 2 (HSV-2) express a type-specific virion structural antigen(s) and that this antigen(s) is present in the envelope of the virus particles. Antisera were prepared in rabbits against HSV-1- and HSV-2-transformed L cells, thymidine kinase-less L (Ltk-) cells, and human embryonic lung (HEL) cells lytically infected for 18 hr with HSV-1 or HSV-2. Both types of virions were purified from African green monkey kidney cells (CV-1) infected for 18 hr with either HSV-1 or HSV-2, and labeled with 3H -thymidine. Antisera prepared against Ltk- cells transformed

to the tk+ phenotype by HSV-1 or HSV-2 preferentially agglutinated purified homologous virions. Transformed cell antisera were much less effective in agglutinating nucleocapsids than they were in agglutinating envelope material from the homologous virus. Antiserum prepared against untransformed Ltk- cells agglutinated about two times as much virus as did preimmune serum, but only 13%-19% as much as was agglutinated by transformed cell antisera. These results indicate that both HSV-1 and HSV-2-transformed L cells express an HSV type-specific structural antigen(s) and that this antigen is present in the virus envelope. Since the transformed cell antisera also agglutinated the heterologous virus but to a lesser extent than the homologous virus, these antisera were capable of detecting type-common antigenic determinants as well. (9 refs.)

77-0985 Malignant Transformation of Rat Embryo Fibroblasts by Herpes Simplex Virus Types 1 and 2 at Suboptimal Temperature. (Eng.) Darai, G. (Institut für Medizinische Virologie, Universität Heidelberg, Im Neuenheimer Feld 324, 6900 Heidelberg, W. Germany) Braun, R.; Flugel, R. M.; Munk, K. *Nature* 265(5596): 744-746; 1977.

The malignant transformation of Sprague-Dawley rat embryo fibroblasts (REF) by herpes simplex virus (HSV) was assessed. Three HSV strains, HSV-1-Thea, HSV-2-Müller and HSV-2-HG-52, were propagated on human fibroblast cells. REF monolayer cultures in the fifth tissue culture passage were infected with HSV-1 or HSV-2 at a multiplicity of infection of five plaque-forming units per cell. After 1 hr of incubation at 37 C, the infected cells were shifted down to a suboptimal temperature of 20 C. Ninety percent of the cells survived the incubation at 20 C. Transformation efficiency was approx one colony per 10^5 original floating cells, corresponding to the formation of one colony per 10^6 HSV-infected REF. The modal chromosome number of the transformed cell clones was > 42 , the modal number of primary rat cells. The spindlelike transformed cell clones grew in soft agar. The capacity of the isolated HSV-transformed clones to induce tumors in rats was evaluated. Newborn Sprague-Dawley rats, 1-2 days old, were inoculated with either normal or transformed REF cells, 1×10^6 to 1×10^8 cells per rat. Animals were observed at least twice weekly for the development of palpable tumors at the inoculation site. The two spindlelike transformed cell lines were highly tumorigenic in syngeneic animals. The induced tumors grew very rapidly and induced metastases in the lung. Histopathologically, the tumors were immature spindle-cell sarcomas. No regression of tumor growth was observed. The detection of HSV antigens in the isolated cell clones and cell lines derived from the tumors was investigated by indirect immunofluorescence, using hyperimmune rabbit antisera. The in vitro transformed cell clones with spindlelike morphology showed cytoplasmic HSV immunofluorescence. In contrast, the epitheliallike cell clone demonstrated very weak fluorescence. Cells derived from the tumors also exhibited HSV cytoplasmic immunofluorescence comparable with that of the original in vitro transformed cells. In conclusion, REF inoculated with HSV-1 or HSV-2

re transformed when the cells are incubated at the suboptimal temperature of 20 C for the first 3 wk after infection. (20 refs.)

7-0986 Herpes Simplex Virus Nuclear Nonviral Antigens Detected by Anticomplement Immunofluorescence. (Eng.) Tarro, G. (Div. Virology, Cattedra di Virologia Oncologica, 1a Facolta di Medicina e Chirurgia, Ospedale "D. Cotugno," Naples, Italy) Giordano, G. G.; Tripodi, A.; Cerra, R.; Di Gioia, M.; Battista, A.; Smeraglia, R. *Tumori* 62(6): 609-614; 1976.

Guinea pig kidney (GPK) cell cultures and WI-38 cells were infected with at least 5 plaque-forming units of herpes simplex virus (HSV) type 2 per cell for 90 min and treated for 8 hr with 20 µg/ml cytosine arabinoside (Ara-C) to block structural antigen formation. The infected cells were then examined by an anticomplement immunofluorescence (ACIF) technique to detect HSV nuclear nonviral antigens. The antiserum was taken from a guinea pig hyperimmunized with a cell suspension harvested 3 hr after the infection with HSV. The complement was from a donor with HSV antibodies. Positive results were obtained with the HSV-infected WI-38 and GPK cells. The appearance of a nuclear antigen detected with the HSV nonviral sera by the ACIF technique permits the extension of this finding to transformed cells and to tumors in which an etiologic relationship with HSV is suggested. This antigen may also be used to monitor the presence of specific antibodies in the sera of patients with different tumors of the oral and urogenital tract. (15 refs.)

7-0987 Herpes Simplex Virus Type 2 and Cancer of the Prostate. (Eng.) Herbert, J. T. (Cancer, Birth Defects Div., Bureau Epidemiology, Center Disease Control, Atlanta, GA 30333) Birkhoff, J. D.; Feorino, P. M.; Caldwell, G. C. *J Urol* 116(6): 611-612; 1976.

A seroepidemiologic study was done on the possible relationship between herpes simplex virus type-2 (HSV-2) and prostatic cancer. Analysis of serum from 28 patients with untreated carcinoma of the prostate and from 20 patients with benign prostatic hypertrophy revealed no significant difference in HSV-2 antibody levels of the two groups. In both groups, approx 70% of the patients had positive titers. HSV-2 should not be excluded as an etiologic factor. Further studies are necessary using a control group of men over 55 yr old who do not have prostatic cancer or hypertrophy because it is possible that both of these conditions stem from the same cause. A prospective study of men between the ages of 35-45 yr is also recommended to determine whether previous HSV-2 infection increases the risk for prostatic cancer. (24 refs.)

77-0988 Laser Flow Cytophotometric Immunoperoxidase Detection of Herpes Simplex Virus Type 2 Antigens in Infected Cultured Human Cells. (Eng.) Leary, J. F. (Dept. Biochemistry and Biophysics, Pennsylvania State

Univ., University Park, PA 16802) Notter, M. F.; Todd, P. *J Histochem Cytochem* 24(12): 1249-1257; 1976.

Herpes simplex virus type 2 (HSV-2) antigens in infected cultured human cells (HEp-2) are detected by laser flow cytophotometric immunoperoxidase. Six hr after HSV-2 infection of HEp-2 cells, staining produced by the indirect immunoperoxidase method using primary antiserum diluted 1:1,000 revealed the presence of intranuclear antigens that were at first near the nuclear envelope but that later converged at the center of the nucleus. Twelve hr after infection, the nuclei were strongly stained, and diffuse cytoplasmic staining revealed the presence of small amounts of viral antigens in the cytoplasm. After 18 hr, both the nucleus and cytoplasm of infected cells were stained, while after 24 hr only the cytoplasm demonstrated evidence of viral products. In the Cyto-graft analysis, the histograms showed that differences in light-scattering properties as measured by the immunoperoxidase method began to appear less than 12 hr after infection. Positive reactions were obtained with primary antibody dilutions ranging between 1:100 and 1:50,000. The 1:10,000 dilution yielded the clearest positive reaction. Localized polymerization of stain at the site of viral products at 6 and 12 hr postinfection caused refractive-index gradients leading to increased wide-angle diffraction. As infection-related antigens increased and the staining pattern after 18 hr became more generalized, the refractive index of the cell became more uniform. As a result, wide-angle diffraction decreased, and increased refraction-related scattering caused the scattering pattern to be moved inward toward the small-angle sensor, thereby reducing the large-angle sensor signal. After 18 hr, the effect of herpes virus infection was to reduce the large-angle scattered light intensity due to the staining of large numbers of intracellular antigens. As the multiplicity of infection was increased, the peak channel number of light scattering decreased, indicating that the large-angle light scattering decrement was a true indicator of the amount of antigen per cell. The study demonstrates the existence of an immunoenzymatic method for the detection of virus infection by flow cytophotometry. (30 refs.)

See also

* (Rev.): 77-0607, 77-0652, 77-0653, 77-0654, 77-0655, 77-0656, 77-0657, 77-0658, 77-0659, 77-0660, 77-0661, 77-0662, 77-0663, 77-0664, 77-0665, 77-0666, 77-0667, 77-0668, 77-0669, 77-0670, 77-0671, 77-0672, 77-0673, 77-0674, 77-0675, 77-0676, 77-0677, 77-0678, 77-0679, 77-0680, 77-0681, 77-0682, 77-0683, 77-0684, 77-0685, 77-0686, 77-0687, 77-0688, 77-0689, 77-0690, 77-0691, 77-0720, 77-0724, 77-0730, 77-0743, 77-0767.

* (Chem.): 77-0813, 77-0824.

* (Phys.): 77-0865.

* (Immun.): 77-0991, 77-0995, 77-1000, 77-1002, 77-1008, 77-1009, 77-1016, 77-1017, 77-1018, 77-1034, 77-1035, 77-1036.

* (Path.): 77-1051, 77-1074, 77-1084, 77-1103, 77-1107, 77-1128.

* (Epid.-Biom.): 77-1171

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77-0989 Role of Polymorphonuclear Leukocytes in Host Defense Mechanism Against Cancer. (Eng.)

Townsend, C. M. (Div. Oncology, Dept. Surgery, Univ. California, Los Angeles, CA) Eilber, F. R.; Chee, D. O.; Morton, D. L. *Surg Forum* 27: 119-120; 1976.

The effect of peripheral blood polymorphonuclear WBC on cultured human normal cells and tumor cells in vitro was studied. Five normal human cell strains (2 embryonic, 3 adult) and four human tumor cell lines (2 melanoma, 1 lung, 1 sarcoma) were used as target cells. WBC from 21 normal donors and 20 cancer patients with various types of tumors were obtained from the peripheral blood. Target cells (1×10^5 /well) were placed in tissue culture plates and, after 4 hr (allowance for cell adherence), 1×10^6 WBC were added. Control wells contained target cells alone. The plates were incubated for 24 hr. The plates were then rinsed, fixed, and stained, and the staining density was graded from 0 to 4+. Disruption of the normal cell monolayer was produced in only 2/74 tests with normal WBC and 4/58 tests with WBC from cancer patients. In all instances, this reaction was observed with one of the embryonic strains. This was in contrast to the effects of normal and cancer-patient WBC on tumor cell monolayers. Disruption was produced by WBC from normal donors in 59/69 tests and by WBC from cancer patients in 46/66. Normal fibroblasts were available for paired testing for both of the melanoma cell lines. None of 13 normal WBC and 0/18 cancer WBC reacted to the fibroblasts, but 13/13 normal WBC and 15/18 cancer WBC reacted to the melanoma target cells. When the ratio of effector:target cells was increased from 10:1, this differential effect was not observed. The effect apparently involves membrane contact, because neither 24-hr culture supernatants nor cell-free distilled water lysates of WBC affected the tumor cells. The study shows that peripheral blood WBC from both normal donors and patients with cancer can discriminate between normal and malignant tissue cultured cells in vitro. (no refs.)

77-0990 Selective Induction of Solid and Ascitic Carcinoma of the Exocrine Pancreas by the Prolonged Action of Heterologous Antiesterase Lipoprotein from Antisera to a Crude Lipoprotein Lipase in Mice. (Fre.)

Andre Thomas, J. (Centre de Physiologie cellulaire, Université Pierre-et-Marie-Curie, 7, quai Saint-Bernard, 75005 Paris, France) *C R Acad Sci (Paris) D* 284(7): 589-593; 1977.

The carcinogenic effect on the mouse pancreas of immune sera obtained from sheep inoculated with crude lipoprotein lipase extracted from rabbit adipose tissue was studied. Injections of the lipoprotein lipase antigen directly did not have a carcinogenic effect in the CD and Swiss mice, even when

repeated every 14 days for several months. After total absorption by normal rabbit serum, several sera with different antilipoprotein lipase activity were obtained from the inoculated sheep. Doses of 0.25-0.50 ml of the immune sera were injected ip every 14 days into the mice for several months. Control mice, injected with 0.5 ml of serum, were observed for 68-283 days. The two most active carcinogenic sera induced death from malignant growth of the pancreas in 45/45 and 10/10 mice in max of 97 days. The next most-active sera produced death in 14/15 mice in 100-213 days and in 11/20 mice in 76-294 days. The least carcinogenic sera caused death in about 21% of the mice in which they were used. After an initial temporary period of lysis, the pancreas appeared adenomatous, with interstitial edema and cellular dedifferentiation (17th day, 7 injections). Malignant changes appeared first in the peripheral zones and consisted of anaplastic clear cells, many in the process of abnormal mitoses. The final stage was characterized by true metastases, at first in the lymph nodes and mesentery, but later in the thymus, ovary, kidney, epididymus, and gastrointestinal tract. It is concluded that a selective carcinogenesis of high incidence induced by an immunologic mechanism is reported for the first time. (7 refs.)

77-0991 Effect of Heterologous Antimacrophage Serum on Growth of Rous Virus-induced Sarcoma in the Allogeneic and Syngeneic System. (Eng.)

Holan, V. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 166 10 Prague, Czechoslovakia) Chutna, J.; Hasek, M. *Neoplasma* 24(1): 63-69; 1977.

The role of macrophages in immune reactions was examined in vivo by studying the effect of heterologous antimacrophage serum (AMS) and normal rabbit serum (NRS) on the immune reaction against Rous virus-induced sarcoma (RSL) in rats. The growth of RSL transplanted against the H-1 barrier in AMS-treated rats was more progressive than in untreated or NRS-treated controls. RSL growth was significantly suppressed in syngeneic AMS- or NRS-treated recipients compared to untreated controls, but neither serum was cytotoxic toward RSL cells. Because AMS and NRS considerably suppressed antibody production with little or no cytotoxic effect on T cells, it is assumed that the progressive growth of a syngeneic sarcoma is facilitated by the function of blocking of macrophage function and thus to an increase in the immune response to tumor-specific antigen and subsequent retardation in tumor growth. These results indicate that partial inhibition of macrophages (regardless of the mediator) results in modifications of the transplantation and antitumor immune reactions. (23 refs.)

77-0992 **Antibody-mediated Suppression of Tumor Growth I. Suppression by Murine IgG1 Isolated from Alloantisera.** (Eng.) Johnson, R. J. (Dept. Microbiology, The Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Pasternack, G. R.; Shin, H. S. *J Immunol* 118(2): 494-497; 1977.

The isolation of immunoglobulin G1 (IgG1) and its tumor-suppressive activity for the murine lymphoma 6C3HED in HeB/Fe and C57BL/6 mice are demonstrated. IgG1 was isolated from hyperimmune alloantisera against the lymphoma by absorption with heat-killed, formalinized *Staphylococcus aureus*, followed by DEAE ion exchange chromatography and Sephadex G-200 gel filtration chromatography. The isolated IgG1, which had no detectable IgM, IgA, IgG2a, IgG2b, or IgG3, suppressed tumor growth. Mouse IgE and specific macrophage arming factor also did not participate in the suppression. The heat stability of the IgG1 suppressive activity was determined to be up to 56°C for 30 min. (22 refs.)

77-0993 **Antibody-mediated Suppression of Tumor Growth II. Macrophage and Platelet Cooperation with Murine IgG1 Isolate from Alloantisera.** (Eng.) Johnson, R. J. (Dept. Microbiology, The Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Pasternack, G. R.; Shin, H. S. *J Immunol* 118(2): 494-497; 1977.

The relationships between the cellular and humoral factors involved in antibody-mediated suppression of tumor growth in vivo, specifically, the effector cells cooperating with immunoglobulin G1 (IgG1) antitumor antibody, were studied. Strains C3HeB/FeJ (C3H) and C57BL/6J (B6) mice received 100 rads of whole-body radiation from a cobalt-60 source. Macrophages, lymphocytes, and platelets were tested with IgG1 antibody to determine their role in IgG1-mediated tumor suppression. The macrophages were isolated from peritoneal exudates induced by injecting mice ip with thioglycollate. The lymphocytes were isolated from peritoneal exudates induced by starch hydrolysate. The platelets were isolated from blood collected by cardiac puncture of ethered mice. Macrophages and platelets were active in reconstituting IgG1-mediated tumor suppression in irradiated hosts. Lymphocytes were not active. All, however, were active with whole antiserum. (17 refs.)

77-0994 **Antibody-mediated Suppression of Tumor Growth. III. Molecular Assay of Murine IgG1 Antibody Required to Cause Tumor Suppression In Vivo.** (Eng.) Johnson, R. J. (Dept. Microbiology, The Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Pasternack, G. R.; Drysdale, B. E.; Shin, H. S. *J Immunol* 118(2): 498-504; 1977.

To determine the number of IgG1 antibody molecules required to mediate tumor suppression in vivo, the number of IgG1 antibody molecules bound to tumor cells injected into male and female BALB/c mice was determined by an IgG1-specific radioimmunoassay. The ratio of radiolabeled anti-IgG1 per cell-bound IgG1 was ascertained by reacting anti-IgG1 with TNP-coupled tumor cells that had a known number of radiolabeled IgG1 anti-DNP molecules bound to them. Standard tumor growth curves made it possible to quantitate the percentage of tumor growth suppression caused by IgG1. Between 70,000 and 130,000 molecules of IgG1 antibody bound per tumor cell were sufficient to cause 50% suppression of tumor cell growth. The number of tumor cells injected per mouse ranged from 41,200 to 67,500. The materials used and techniques are described in detail. (17 refs.)

77-0995 **The Autoreactivity of Splenocytes in Mice of Sensitive Lines in the Latent Period of Carcinogenesis Induced by SA7(C8) Virus.** (Rus.) Ageenko, A. I. (P. A. Gertsen Moscow Scientific Res. Inst. Oncology, Moscow, USSR) Erkhov, V. S. *Vopr Virusol* (6): 734-737; 1976.

Antibodies to antigens of embryonic fibroblasts in CBA mice (susceptible to oncogenesis) and C57BL/6 mice (not susceptible to oncogenesis) were investigated and identified. The mice were inoculated with SA7(C8) virus (0.1 ml of a 10^{-4} dilution, sc) within 24 hr of birth. RBC were separated from the spleen cells 20-30 days after virus treatment and labeled with ^{51}Cr ($30 \mu\text{Ci}/10^6$ cells). The cells (2.5×10^6) were washed and placed in test tubes with monolayers of embryonic fibroblasts for 4 hr and adsorption was measured. Spleen cell antibodies to antigens of embryonic fibroblasts increased in CBA mice. These antibodies were absent from C57BL/6 mice. The difference between the experimental and control groups was > 0.1 . The splenocytes of intact CBA mice were adsorbed on embryonal fibroblast monolayers at a rate of 9.8% for virus-treated cells and 4.2% for untreated cells (controls). (12 refs.)

77-0996 **Tissue Antibodies in Malignant and Benign Urogenital Disease.** (Eng.) Kurki, P. (Dept. Serology and Bacteriology, Univ. Helsinki, 00290 Helsinki 29, Finland) Linder, E.; Miettinen, A.; Alfthan, O.; Heikkinen, A.; Pasternack, A. *Int J Cancer* 19(3): 332-336; 1977.

The presence of antitissue antibodies in sera from patients with nonmalignant genitourinary diseases and genitourinary carcinomas was examined by indirect immunofluorescence. The patients with chronic kidney inflammation and urogenital cancer had a higher incidence of smooth muscle, rabbit bile canaliculi, antinuclear, and reticulin antibodies than did controls. A total of 84/110 cancer patients and 40/100 controls had detectable tissue antibodies in the serum. Twenty-

four patients with cancer, 12 with chronic renal inflammation, and 11 controls were positive for smooth muscle antibodies reacting with glomeruli. Muscle antibodies reacting with vessel walls were detected in the serum of 15 cancer patients, 4 patients with chronic renal inflammation, and 7 controls. There was an association between metastatic undifferentiated tumors and antinuclear antibodies. An increased incidence of tissue antibodies was noted in carcinomas of the kidney, prostate, and urinary bladder. Antibodies against connective tissue reticulin were correlated with a low degree of malignancy. Inflammation is a significant factor in tissue antibody production. (19 refs.)

77-0997 Heavy-Chain Variable-Region Sequence from an Inulin-Binding Myeloma Protein. (Eng.)

Vrana, M. (Lab. Cell Biology, NCI, NIH, Bethesda, MD 20014) Rudikoff, S.; Potter, M. *Biochemistry (Washington)* 16(6): 1170-1175; 1977.

As part of a study of the antigenic determinants of myeloma proteins, the structure of five inulin-binding proteins is being studied. The entire variable-region sequence of the heavy chain from ABE-47N, a BALB/c inulin-binding mouse myeloma protein, was determined. This protein is unusual in that the third complementarity region (H3) is extremely short, consisting of at the most three and probably only one amino acid. A comparison of the heavy-chain hypervariable regions from mouse, human, and rabbit proteins shows that the variability in length of H3 is greater than that seen in the first or second hypervariable regions. This variability in H3 length suggests a specialized function for this region. Compared to H3 of other species, the H3 from these mice is very short. The size variations of H3 may be important in the generation of functional antibody diversity. (30 refs.)

77-0998 Ligand-Induced Redistribution and Augmentation of Surface-Bound Myeloma Protein on MOPC315 Plasmacytoma Cells. (Eng.)

Hannestad, K. (Inst. Medical Biology, Univ. Tromsø Sch. Medicine, Tromsø, Norway) *Scand J Immunol* 6(1-2): 59-76; 1977.

The ligand-induced redistribution of surface-bound, trinitrophenyl (TNP)-binding IgA myeloma protein M315 on plasmacytomas grown in BALB/c mice was investigated. When MOPC315 wild-type plasmacytoma cells were incubated at 37 C with saturating amounts of TNP₁₄-BSA (bovine serum albumin, 20 µg/ml) or bivalent antisera specific for M315, small, evenly distributed fluorescent spots were seen on 100% of cells after 30 min. Longer incubation resulted in irregular patches, and up to 30% had one or more polar caps after 5 hr. Similar staining patterns were observed with the L chain-producing MOPC315 VAR (tumor variant) cells,

using rabbit antiserum that precipitates L³¹⁵ (the L chain of M315). When cells were incubated with saturating concentrations of TNP₁₄-BSA or BALB/c anti-M315 idiotype antiserum for 1 to 3 hr, the spots produced at 37 C were larger and more intense than those formed at 4 C. Thus, secretion may be necessary for the surface expression of M315. When cells were placed in diffusion chambers and implanted peritoneally in BALB/c mice with serum-binding capacity for M315, spotting still occurred. After the transfer of chambers from immune to nonimmune mice, the clearance of spots and reappearance of free myeloma protein were much slower for plasmacytoma cells than for B cells. Cells that were pretreated for 1/2 hr at 37 C with 0.33 mg/ml anti-IgA bound eight times more TNP-BSA than cells preincubated at 37 C in medium alone. In contrast, pretreatment at 4 C increased binding only twofold. When M315 reacts with cross-linking ligand, its release is inhibited, leading to a prolonged lifetime on the membrane. Large immune complexes, to which secretory Ig contributes a great deal, may be anchored to the membrane by a few (6×10^3) M315 molecules. Accumulation of myeloma protein with cross-linking antibodies may provide favorable conditions for an antibody-mediated attack on the tumor. (42 refs.)

77-0999 Structural Studies of Human Immunoglobulin D Myeloma Proteins: Circular-Dichroic Studies of Two Intact Proteins and Enzymatically Derived Fragments. (Eng.)

Jefferis, R. (Dept. Experimental Pathology, Medical Sch., Vincent Drive, Birmingham B15 2TJ, England) Matthews, J. B.; Bayley, P. *Biochem Soc Trans* 5(1): 279-282; 1977.

The circular dichroism spectra of two intact human IgD myeloma proteins and of their fragments (Fabδ and Fcδ after trypsin digestion) were studied. The absorption band at 235 nanometers was found to be a feature of the Fabδ fragment of protein Ai. IgD appears to have a unique enzyme digestion pattern and to be susceptible to conformational change within the Fabδ and Fcδ regions. These features are consistent with the function of membrane-bound receptor proposed for IgD. (13 refs.)

77-1000 Polyclonal Ig Production after Epstein-Barr Virus Infection of Human Lymphocytes In Vitro. (Eng.)

Rosen, A. (Dept. Tumour Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden) Gergely, P.; Jondal, M.; Klein, G.; Britton, S. *Nature* 267(5606): 52-54; 1977.

Lymphocytes from cord blood and adult peripheral blood were exposed to Epstein-Barr virus (EBV) in vitro, and the amount of immunoglobulin M (IgM) released was measured. This was done to test the hypothesis that the virus triggers the infected cells to release Ig. The IgM released was determined by double-antibody radioimmunoassay, and individual

antibody-forming cells (PFC) against haptenated RBC and sheep RBC were also measured. Following infection with B95-8 EBV, DNA synthesis was increased significantly over the noninfected controls. IgM was detected from the third day on and it increased in most cultures by a factor of 10 until day 7. Lymphocytes stimulated with fetal calf serum and lymphocytes from adult EBV-positive donors also produced detectable IgM, but at significantly lower levels than the virus-stimulated cultures. The radioimmunoassay results were confirmed by using monospecific antibodies against μ , γ , κ , and λ chains to precipitate Ig from spent media from infected and control cultures. The four antisera showed significant precipitation values, indicating that the Ig produced is polyclonal. EBV-exposed cord blood lymphocytes were able to generate direct PFC against both haptenated RBC and sheep RBC after 6 days of culture. The data showed that human newborn and adult peripheral blood contains cells that can be stimulated to produce antibodies. (20 refs.)

77-1001 Quantitative Determination of Immunoglobulins on the Cell Surface in a Case of Burkitt's Acute Leukemia (Letter to Editor). (Fre.) Follezu, J. Y. (Laboratoire d'Hématologie (C.N.R.S. - E.R.A. n 500), C.H.U. Pitie Salpetriere, 91, boulevard de l'Hopital, F 75634 Paris Cedex 13, France) Andrieux, J. M.; Roisin, J. P.; Dighiero, G.; Schaison, G. *Nouv Presse Med* 5(40): 2717; 1976.

Burkitt's leukemia was diagnosed in a 16-yr-old girl who presented with voluminous cervical adenopathy, an enlarged tonsil, hepatosplenomegaly, and nodules in both breasts. Blood studies showed anemia and WBC count of 38,900/mm³, of which 84% were blasts. Vacuolated blasts (Burkitt's cells) composed 85% of the iliac bone marrow, and they were found in the cervical nodes and breast nodules. The patient died 8 days after initiation of treatment with prednisone, cyclophosphamide, vincristine, and blood transfusions. Specific human immune serums demonstrated surface immunoglobulins (IgS) of the kappa light chain IgM type on 100% of the blast cells. Quantification revealed an av of 85,000 antigenic sites per positive cell, a number significantly higher than that observed for lymphocytes in chronic lymphoid leukemia (9,000 sites/cell), but similar to that of lymphocytes in prolymphocytic leukemia or acute transformation of chronic leukemia. IgS may have prognostic significance in lymphoproliferative syndromes. (5 refs.)

77-1002 Characterization of Immunoglobulins Eluted from Hamster SV40 Tumors. (Eng.) Goldrosen, M. H. (Dept. General Surgery, Roswell Park Memorial Inst., Buffalo, NY) Dent, P. B. *Immunol Commun* 6(2): 133-147; 1977.

Low-pH elutions were performed on autochthonous and transplantable simian virus 40 (SV40) tumors growing in situ

for various lengths of time (14-162 days) to determine if antibodies directed to cell surface antigens were absorbed onto the tumor surface. Ouchterlony analysis revealed that immunoglobulin G₂ (IgG₂) was present in all tumor eluates but that IgG₁ was present only in eluates from tumors that grew in situ for > 60 days. IgA was present in 5/8 eluates tested and IgM in 6/8 eluates, but their presence did not correlate with the duration of in situ growth. No antibodies to cell surface antigens were detected, but antibodies directed to the SV40 nuclear T antigen were detected in all the eluates of H50 cells (SV40 virus-induced hamster tumor cell line). The tumor eluates did not block the in vitro lymphocyte-dependent microcytotoxicity of immune lymphocytes against cultured SV40 tumor cells. Although no evidence was found to indicate that the IgG₁ eluted from the tumors has any growth-promoting properties, its association with tumors present for prolonged periods raises the possibility that the IgG₁ response may be associated with a more favorable outcome to the tumor-host interaction. (27 refs.)

77-1003 IgG Subclasses in Malignant Melanoma. (Fre.) Daveau, M. (Centre departemental de Transfusion sanguine, 76230 Bois-Guillaume, France) Pavie-Fischer, J.; Rivat, L.; Ropartz, C.; Peter, H. H.; Cesarini, J. P.; Kourilsky, F. M. *Ann Immunol (Paris)* 128C(1/2): 113-116; 1977.

Immunoglobulin G (IgG) levels were measured in 397 serum samples from 185 patients with malignant melanoma. The patients were divided into three groups on the basis of the extent of their disease: Stage I, primary tumor and no metastases; Stage II, recurrence of primary tumor and/or invasion of local lymph nodes; Stage III, distant metastases. Total IgG did not differ in the three groups, and it was within normal limits. The subclasses of IgG, IgG1 and IgG3, also did not differ. Alterations (increase or decrease) in the IgG4 levels were observed in Stage II and Stage III patients, although an increase was more likely in advanced disease. The percentage of abnormalities was 19% for Stage I, 55% for Stage II, and 53% for Stage III. (9 refs.)

77-1004 Some Properties of Monoclonal Cryoglobulin M Appearing in the Course of Malignant Lymphoma with Macroglobulinemia. (Eng.) Tomaszewski, J. (Res. Centre and Dept. Hematology, Medical Sch., ul. Jaczewskiego 8, 20-950 Lublin, Poland) Kowalewski, J.; Ruppeniewska, Z.; Wozniak, K. *Clin Chim Acta* 75(2): 331-335; 1977.

Serum containing monoclonal immunoglobulin M (IgM) was obtained from a 60-yr-old man who had malignant lymphoma with macroglobulinemia. The monoclonal cryoglobulin IgM was separated. Electrophoresis of the purified cryoglobulin identified it as an IgM with a kappa-type light chain. It had a very low hydroxyproline content compared to nor-

mal IgM. The lack of hydroxyproline may affect the solubility and precipitation of cryoglobulin. Deficient polymerization of IgM was found in a patient with increased hydroxyproline-containing peptides; it is hypothesized that the lack of the latter may lead to hyperpolymerization. (26 refs.)

77-1005 Use of β -Microglobulin as a Marker for the Isolation of Tumor Antigens in Humans. (Fre.)

Gold, P. (Dept. Allergy and Clinical Immunology, Montreal General Hosp., Montreal, Quebec, Canada) Rauch, J.; Charbonneau, Y.; Shuster, J. *Ann Immunol (Paris)* 128C(1/2): 469-471; 1977.

Tumor antigens of pulmonary and mammary cancers can be isolated and purified with the use of normal hepatic tissue whose membranes have been digested by papain. Radioactive (^{125}I) β -microglobulin (β -m) is used as a label of the histocompatibility antigen (HL-A). Great heterogeneity has been observed among these antigenic molecules. Tumoral antigenic activity can also be demonstrated by the leukocyte adhesion (LAI) test. Sensitized cells from cancerous patients, when incubated with tumor cells, lose their ability to adhere to glass. The tumoral antigenic activity of cancer cell membranes is found repeatedly in the fraction containing β -m, except when the latter is present in the free state. Cell membranes from mammary epitheliomas, after digestion by papain, possess a tumoral antigenic activity that is shown by the LAI test. The effluent fraction contains only minimal microglobulin activity and no tumoral antigenic activity. The eluant contains all the microglobulin activity and strong tumoral antigenic activity. There seems to be a similarity between mammary cancer antigens and HL-A antigens. Repetition of these studies with pulmonary cancers, malignant melanomas, and hepatomas has given the same results. (no refs.)

77-1006 Shared Antigens Between Animal and Human Tumors and Microorganisms. (Eng.) Minden, P.

In: BCG in Cancer Immunotherapy. Lamoureux, G.; Turcotte, R.; Portelance, V., eds. (New York: Grune & Stratton, Inc.): pp. 73-81; 1976.

Studies of the possibility that antigenic components are shared by BCG and certain neoplastic cells are described. Reactions between two kinds of radiolabeled antigens derived from BCG and melanoma cells and two kinds of antisera (anti-BCG and antimelanoma) were inhibited after the sera were preincubated with unlabeled BCG-SS (a soluble extract prepared from BCG) and after they were absorbed with intact melanoma cells. Antigens in melanoma cells from the five patients tested shared antigenic components with BCG-SS. Human neuroblastoma cells and acute myeloid leukemia were shared antigens with BCG. Of the tumors that share

antigens with BCG, all have been reported to respond to BCG with the exception of neuroblastoma, which has not yet been tested for this response. If the sharing of antigens between tumor cells and microorganisms is widespread, the possibility exists that microorganisms could be selected for the specific immunotherapy or prophylaxis of some tumors. It is also speculated that effective immunologic responses to some tumor antigens depend, in part, on a preexisting state of sensitization to microorganisms. (47 refs.)

77-1007 Synergistic Lymphocyte Stimulation to Tumor Specific Antigens After Immunization with Modified Tumor Cells. (Eng.) Enker, W. E. (Dept. Surgery Univ. Chicago, Chicago, IL) *Surg Forum* 27: 154-157; 1976

The comparative effect of *Vibrio cholerae* neuraminidase (VCN) and concanavalin A (Con A) as cell surface modifiers in relation to antigen-specific lymphocyte stimulation was studied. Syngeneic, 12-wk-old, Wistar Furth rats were immunized with either Minimal Essential Medium, unmodified syngeneic tumor cells (WFCC-3 adenocarcinoma of the colon), VCN-modified tumor cells, or Con A-modified tumor cells once weekly for 2 wk with 10^7 cells. All cells received 5,000 R of high-voltage radiation. One week later, quadruplicate samples of 5×10^5 lymph node cells from the immunized hosts were placed in round-bottomed wells with either $1 \mu\text{g}$ well of Con A, 10^5 or 5×10^4 mitomycin-blocked WFCC-3 cells, or control cells of the Morris hepatoma 5123. Tumor cells and mitogens were not utilized together as stimulators. Lymphocyte stimulation was assessed on days 3 and 4 by liquid scintillation counting 24 hr after the addition of $1 \mu\text{Ci}$ of ^3H -thymidine to each well. On day 3, no stimulation was evident in lymph node cells from media-immunized animals that were incubated with MH5123 cells. Antigenic stimulation was evident in the lymph node cells from VCN-tumor cell-immunized or unmodified-tumor cell-immunized rats that were incubated with the graded doses of WFCC-3 cells. The tumor-immunized hosts also responded to the control of MH5123 cells. However, animals immunized with Con A-modified tumor cells responded only minimally on day 3 with no stimulation induced by MH5123. On day 4, a peak stimulation of up to 13.69 was evident in lymph node cells from Con A-modified tumor cell-immunized rats incubated with syngeneic WFCC-3 cells, without a concomitant stimulation by the control MH5123 cells. The results indicate that both VCN and Con A increase antigenic recognition by immunized hosts to syngeneic tumor antigens. The kinetics of these responses differ, implying possible differences in mechanism. (3 refs.)

77-1008 Antigenic Deletion and Malignant Enhancement Induced in Lymphoma Cells by Passage Through X-Irradiated Hosts. (Eng.) Ioachim, H. L. (Dept. Pathology, Lenox Hill Hosp., New York, NY 10021) Pearce A.; Keller, S. E. *Nature* 265(5589): 55-57; 1977.

maligant enhancement and antigenic deletion induced in lymphoma cells by passage through x-irradiated hosts are investigated. The lymphoma cells that were used were taken from W/Fu rats injected at birth with Gross leukemia virus (GLV). The cells were obtained either fresh from rat thymomas or from an established LT₁ lymphoma tissue culture line that permanently replicated GLV. In rats given 300-350 R total body x-irradiation, lymphoma cells transplanted within 4 hr sc or ip grew progressively at the site of the graft, spread to distant sites occasionally, and eventually caused the death of the hosts. Lymphoma cells from such tumors growing in x-irradiated rats were then transplanted into normal, adult, syngeneic recipients, and in contrast to lymphoma cells of thymomas and of tissue cultures were not rejected but grew into large tumors that metastasized widely and killed the recipients. Only 10-20% of lymphoma cells from tumors growing in the x-irradiated rats showed ringlike membrane fluorescence, while approx 60% displayed capping of fluorescence and 20% of the cells had become entirely negative. Tumors examined at longer intervals after transplantation in x-irradiated rats demonstrated a progressive increase in the number of capped and negative cells with a proportionate decrease in the number of cells with positive ringlike fluorescence. Examined under the electron microscope, the transplantable lymphoma cells appeared devoid of both mature and immature virus particles. Cytotoxicity assays were carried out utilizing serum of rats that had rejected murine leukemia virus (MuLV)-positive lymphoma cells against MuLV-negative lymphoma cells as target cells and MuLV-positive lymphoma cells as controls. The results confirmed the lack of MuLV antigenic expression on the transplantable lymphoma cells. There were higher anti-MuLV antibody titers (up to 1:4,096) in the normal recipients grafted with MuLV-cells that grew into progressive tumors than in those grafted with MuLV+ cells that were rejected. The deletion of membrane viral antigens may be the result of antigenic modulation. (21 refs.)

77-1009 T-Cell-Dependent Reactivity Against Tumor-Associated Antigens on Allogeneic Target Cells. (Eng.) Holden, H. T. (Lab. Immunodiagnosis, NCI, Bethesda, MD 20014) Landolfo, S.; Herberman, R. B. *Transplant Proc* 9(1): 1149-1152; 1977.

T-cell-dependent reactivity was evaluated in a primary murine sarcoma virus (MSV)-induced tumor system. In vitro secondary-response experiments were set up to determine whether presensitized T lymphocytes could be restimulated by tumor-associated antigens to develop cytotoxic reactivity if the antigen was presented on an allogeneic cell. Cytotoxic activity against syngeneic tumor target cells was induced in C57BL/6 immune spleen cells by either syngeneic or allogeneic stimulator cells. Normal spleen cells did not develop high levels of activity against syngeneic targets when incubated with syngeneic or allogeneic tumor cells. If MSV-immune, BALB/c responding cells were employed, there was a differ-

ent pattern of reactivity. Cytotoxicity was detected against the syngeneic Moloney-induced tumor only if the spleen cells were stimulated with Moloney virus-induced lymphomas with the same H-2 expression. When allogeneic Moloney-induced tumors were used as stimulating cells, there was no increase in activity. The reactivity of C57BL/6 spleen cells against allogeneic target cells was reduced quantitatively by the addition of either syngeneic or allogeneic tumor cells. Specifically, immune T lymphocytes can interact with tumor-associated antigens on allogeneic and syngeneic target cells. (12 refs.)

77-1010 Multiple Foreign Non-H-2 Determinants on the Surface of a Chemically- Induced Murine Sarcoma. (Eng.) Invernizzi, G. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy) Carbone, G.; Meschini, A.; Parmiani, G. *J Immunogenet* 4(2): 97-106; 1977.

The presence of foreign non-H-2 transplantation antigens acting as tumor-associated transplantation antigens (TATA) of a methylcholanthrene induced ST5 fibrosarcoma of BALB/c mice was studied. BALB/c mice preimmunized with normal syngeneic BALB/c minced liver and kidney tissues or with normal allogeneic liver and kidney tissues were challenged with ST5 tumor cells. Protection against ST5 cells was obtained for mice inoculated ip with DBA/2 tissues (4/10 mice afflicted, $p < 0.05$); C57BL/6J (2/10 mice afflicted, $p < 0.01$); and C3Hf tissues (1/10 mice afflicted, $p < 0.01$) compared to control BALB/c tissues (8/10 mice). No resistance was induced by AKR normal tissues (10/10 mice afflicted). Lymph node cells from BALB/c mice immune to C3Hf, C57BL/6J, DBA/2 normal tissues and control anti-ST5 tumor-specific lymph node cells inhibited I¹²⁵-iododeoxyuridine (¹²⁵IUdR) uptake by cultured ST5 cells ($p < 0.01$) compared to effector cells from BALB/c mice treated with syngeneic tissues. The involvement of foreign H-2 specificities was eliminated by absorption of H-2 monospecific sera. Using the indirect isotopic antiglobulin assay, C57BL/6J anti-BALB/c serum (control), BALB/c anti-C57BL/6J and anti-C3Hf sera were found to bind to cultured ST5 cells ($p < 0.001$ compared to BALB/c normal serum). No reaction was observed with BALB/c anti-AKR and anti-DBA sera. The anti-ST5 activity of the anti-C57BL/6J serum was absorbed by C57BL/6J lymph node cells and C3Hf lymph node cells but not DBA/2 lymph node cells. The expression of two sets of foreign non-H-2 antigens, one shared by C57BL/6J and C3Hf tissues and the other belonging to DBA/2 tissues is indicated by these results. (23 refs.)

77-1011 Association Between Leucocyte Group-5a Antigen and Acute Lymphoblastic Leukaemia. (Eng.) Warren, R. P. (Fred Hutchinson Cancer Research Center, Seattle, WA) Storb, R.; Nguyen, D. D.; Thomas, E.

D. *Lancet* 1(8010): 509-510; 1977.

Leukocyte group 5 has two dominant alleles (5a and 5b) which segregate independently of the major histocompatibility complex. This group-5 system was studied in a Caucasian population of healthy controls and patients with acute lymphoblastic leukemia (ALL). The controls and patients were not related. The 5a gene frequency was 0.09 in 72 controls and 0.38 in 39 patients with acute lymphoblastic leukemia ($p < 0.001$). In 15 patients with acute myelogenous leukemia and 12 patients with aplastic anemia, the 5a and 5b frequencies were similar to those of the control population. Study of group-5 antigens in 16 families of patients with ALL indicated that the increased frequency of 5a among patients with ALL is inherited and not due to the disease or therapy. Susceptibility to ALL appears to be related to 5a or a closely linked gene. (16 refs.)

77-1012 Confirmation of the Existence of Human Serum Leukaemia-Associated Antigens (LAA). (Eng.)

Berg, K. (Inst. Medical Genetics, Univ. Oslo, Blindern, Oslo 3, Norway) Stavem, P.; Harris, R.; Noer, G.; Molne, K. *Scand J Haematol* 17(5): 388-394; 1976.

The existence of human serum leukemia-associated antigens (LAA) is confirmed. Two rabbits were immunized with a suspension of lyzed amniotic fluid cells. They were each given a total dose of 6.5 ml of the suspension, distributed on four injections. The first injection was given in the foot pads, together with 1 ml complete Freund's adjuvant, and the first booster dose was given 3 wk later. The sera of the rabbits did not contain antibodies similar to that of antiserum R77 after the immunization with fetal cells. Subsequently, these two rabbits were given booster doses of leukemia patient WBC. Both animals were given 2 ml of the suspension of leukemia patient WBC im and bled 6 days later. Both rabbits exhibited precipitating antibodies, and one of the sera (R91) reacted with leukemia patient serum after absorption with normal human serum. The other rabbit antiserum (R90) exhibited a more complex pattern on agar gel precipitation tests. Of the antisera analyzed, only antisera R77, R91 and R90 reacted with leukemia patient serum after absorption with normal sera. Antiserum R90, however, also reacted with normal sera and thus behaved in a distinctly different way from antisera R77 and R91. A total of 38 British leukemia patient sera that had been analyzed with a reference antiserum to LAA was tested with antiserum R77. Antiserum R77 detected an antigen that was closely related, if not identical, to the antigen demonstrable with reference antisera to LAA. Antiserum R91 also correlated positively with LAA antiserum. However, approx 10% of sera from patients with miscellaneous hematological disorders exhibited differences with respect to their reactions with antisera R77 and R91, and the difference was significant. All patient sera that reacted with antiserum R91 also reacted with antiserum R90, whereas no R90 negative serum was positive with antiserum R91. Antiserum R90 contained an additional specificity, reflected by the 40 serum

samples that were positive with antiserum R90, although they were negative with antiserum R91. LAA may be an oncofetal component. (5 refs.)

77-1013 Multiple Composition of Foreign Alloantigens on a Murine Fibrosarcoma. (Eng.) Invernizzi, G. (Div. Experimental Oncology A, Natl. Cancer Inst., Milano, Italy) Carbone, G.; Parmiani, G. *Folia Biol (Praha)* 22(6): 393-394; 1976.

The multiple composition of tumor-associated antigens (TATA) found on a methylcholanthrene induced BALB/c mouse fibrosarcoma (ST5) is discussed. An in vitro serological approach was used in measuring, by an indirect isotopic antiglobulin assay, the amount of binding of mouse BALB/c and C57BL/6J alloantisera to cultured ST5 cells. The BALB/c cells reacted with C57BL/6J anti-BALB/c control serum, BALB/c anti-C57BL/6J and anti-C3Hf sera. No significant binding was observed with BALB/c anti-AKR and anti-DBA/2 sera. Reactivity of BALB/c anti-C57BL/6J serum on ST5 cells was removed by absorption with ST5 cells and with C57BL/6J lymph node cells ($p < .01$ for absorbing dose of 8×10^6 and 16×10^6 cells), and with 16×10^6 C3Hf lymph node cells (significant; p not given). No absorption occurred with DBA/2 lymph node cells or with the unrelated BALB/c sarcoma TZ15. In conclusion, two foreign alloantigens are detectable on ST5 tumor cells: a serologically detected alloantigen of the C57BL/6J strain and a DBA/2 strain detected only by cell-mediated assay--previously observed using a cell-mediated assay in which ST5 cells were highly sensitive to BALB/c anti-DBA/2 lymphocytes. (8 refs.)

77-1014 Expression of H-2K, H-2D and Ia Region Products of Foreign Haplotypes on Mouse Tumour Cells. (Eng.) Garrido, F. (Tissue Immunology Unit, London Hosp. Medical Coll., London, E1, 2AD, England) Festenstein, H. *Folia Biol (Praha)* 22(6): 391-392; 1976.

The appearance of H-2 foreign haplotypes on YAC lymphoma and EL4 leukemia mouse tumor cells is reported. The activity of ^{14}C -thymidine uptake by tumor cells YAC (H-2a, K.23, D.4) and EL4 (H-2b, K.33, D.2) treated with anti-H-2 sera was assayed. Antiserum H-2K.23 used against YAC tumor cells gave an 88% reduction in thymidine uptake; no reduction occurred for EL4 tumor cells. Likewise, anti-H-2D.4 caused a reduction of uptake by YAC and but not by EL4, as expected from the genetic make-up. Unexpectedly, anti-H-2D.2, a private specificity of the haplotype H-2b, caused a 95% reduction of uptake by EL4 and a 91% reduction with YAC, an H-2a derived tumor. Ia antigens were demonstrated on SLA (H-2d) mouse leukemia tumor cells; Ia antigens are mainly found in B-cells and macrophages. These data support a derepression mechanism hypothesis allowing the expression at the cellular surface of extra H-2 allodeterminants recognizable by immunocompetent cells. (8 refs.)

7-1015 **Analysis of Hybrids Between an H-2+, TL- Lymphoma and an H-2+, TL+ Lymphoma and an H-2-, TL- Variant Subline.** (Eng.) Hyman, R. (Dept. Cancer Biology, Salk Inst. Biological Studies, Post Office Box 09, San Diego, CA 92112) Stallings, V. *Immunogenet* 4(2): 1-181; 1977.

The hybrids between an H-2+, TL+ lymphoma and an H-2-, TL- lymphoma were assessed for their expression of TL and H-2 antigens. EL4 had major populations of cells with 40 and 40 chromosomes, with a few cells above and below these numbers. R1(TL+) had a major population of cells with 42 chromosomes and a minor population of cells with 41 chromosomes, but R1(TL-) had a major population of cells with 41 chromosomes and a minor population with 40 chromosomes. Quantitative absorption studies were performed on R1(TL+) x EL4 hybrids. The H-2b haplotype of the EL4 parent and the H-2k haplotype of the R1(TL+) parent were both expressed in these hybrids. The TL3 specificity characteristic of the R1(TL+) parent was retained in the hybrid, and the TL specificity characteristic of C57BL leukemias was not expressed. Nearly all the cells of each R1(TL+) x EL4 hybrid expressed TL1,2,3. Almost all the cells of the hybrids F263.1 and F264.1 expressed H-2b and H-2k. The hybrid F262.1 demonstrated a significant number (approx 30%) of cells that did not show detectable H-2b and a similar number that did not show detectable H-2k. Absorption studies showed that R1(TL-) x EL4 hybrids expressed TL1,2,3 and H-2k, although these antigens were not expressed by either parent. When monospecific anti-TL3 and anti-TL4 sera were used, the hybrids demonstrated a similar expression of TL3 but no detectable expression of TL4. The hybrids expressed private H-2k specificities characteristic of serologically defined antigens coded for by both K- and D-region genes of the H-2k haplotype. The H-2b antigen of the EL4 parent was expressed by all hybrids. Direct cytotoxicity tests on the R1(TL-) x EL4 hybrids showed that nearly all hybrid cells expressed TL1,2,3. Almost all (> 85%) hybrid cells expressed detectable H-2b. Reaction for the H-2k antigen was more variable: > 85% of F314.1 cells expressed detectable H-2k, as did 65%-70% of F310.1 cells, but only 30%-40% of F312.1 cells expressed detectable H-2k antigen. The defect in the variant cell is the result of a mutation affecting the gene coding for an element for expression of TL and the H-2 antigens on the cell surface. (21 refs.)

77-1016 **H-2 Antigen Variants in a Cultured Heterozygous Mouse Leukemia Cell Line.** (Eng.) Rajan, R. V. (Dept. Pathology, Albert Einstein Coll. Medicine, Bronx, NY 10461) *Immunogenet* 4(2): 105-115; 1977.

The H-2 antigen variants in a heterozygous Friend leukemia cell line of the mouse were studied. A single-step selection procedure, utilizing anti-H-2 antibodies in the presence of complement, was used to isolate the H-2 variants. The direct lysis of the b/d Friend cell line and H-2d- clone 1 was

determined. The variant cells were as susceptible as the wild-type cells to anti-H-2b antiserum. The cells remained susceptible to complement-mediated lysis, and they continued to express the unselected antigens. On the other hand, they were completely refractory to lysis using the anti-H-2d antiserum. The variants were examined for the presence of H-2 antigens on the cell surface by the quantitative absorption assay. In an assay for the H-2d antigens, the data indicated that the variants expressed < 0.001 times as much antigen as the wild-type cells. Assays for the unselected antigens coded for by the H-2b haplotype revealed essentially similar amounts on the variants and the wild-type cells. The H-2b-directed T cells lysed the H-2d- clone 1 twice as efficiently as they did the heterozygous b/d line. Lysis of the putative hemizygous variants approximated that of the homozygous H-2b control. Karyotypes of the b/d Friend cells and the H-2d- and H-2b- cells were evaluated. Both the parent and the variants had two copies of chromosome 17, ruling out the possibility of chromosome loss as the mechanism for the origin of the variants. The Robertsonian translocation of the chromosomes 17 was far more frequent in the variants than in the parent (100%, as opposed to 60% in the parent). A small number of the parental spreads (5/50) had an additional marker chromosome not found in any of the variants. This marker did not appear to contain any portion of chromosome 17 in it. Chromosome loss does not seem to be the originating mechanism for the variants. (10 refs.)

77-1017 **H-2 Compatibility Requirements for T Suppressor Cell Functions Induced by Friend Leukemia Virus.** (Eng.) Kumar, V. (Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA 02118) *Nature* 265(5592): 345-347; 1977.

The H-2 compatibility requirement for the suppressive interaction between T suppressor cells and mitogen-responsive cells in cultures infected with Friend leukemia virus (FV) was investigated. It was found that there is an H-2D compatibility requirement. Spleen cell suspensions containing mitogen-responsive cells (but not suppressor cells) from resistant B10.D2, B10.A, and C57BL/6 mice responded well to concanavalin A in the presence of FV. The addition of small numbers (10^5) of H-2-identical or semiallogeneic susceptible spleen cells, containing T suppressor cells, to 9×10^5 spleen cells of resistant mice resulted in the suppression of mitogenesis by FV. The suppressor cells functioned after exposure to 800 R of x-ray in vitro. Suppression across the H-2 barrier was not effective. Adult DBA/2 (H-2d) spleen, marrow, or thymus cells failed to suppress C57BL/6 (H-2b) spleen cells. The findings indicate that donors of cell suspensions containing T suppressor cells and the mitogen-responsive cells must share the same H-2D determinant for FV to induce immunosuppression in vitro. In appropriate conditions in vivo (transfer of resistant marrow cells into irradiated susceptible infant mice previously infected with FV), no H-2 restriction for immunosuppression had been observed in the FV model.

This consideration suggested the possibility that a third cell type, the interfering cell, was responsible for the H-2 restriction. This possibility was confirmed when the H-2D restriction was overcome by irradiating the cell suspension containing T suppressor cells or by the administration of cortisol (an adrenal steroid). The mechanism of interference by the third cell type has yet to be determined, but the release of receptors for alloantigens is one hypothesis under consideration. (22 refs.)

- 77-1018 Role of H-2 Antigens in the Cytolysis of Oncornavirus Induced Tumour Cells by Syngeneic T Lymphocytes.** (Eng.) Gomard, E. (Lab. Tumour Immunology and Virology, INSERM U 152, Paris, France) Duprez, V.; Henin, Y.; Levy, J. P. *Folia Biol (Praha)* 22(6): 387-388; 1976.

The cell-destroying reaction of cytolytic T lymphocytes (CTL) of hybrid (C57BL/6 × BALB/c)F₁(C × B6) mice against an H-2 modified antigen of oncornavirus induced tumor cells is reported. The mice were inoculated with either tumor cells from one parental line or with murine sarcoma virus (MSV). CTL of F₁ hybrid mice immunized against tumor cells reacted only with target cells having the same H-2 antigen as the immunizing tumor. CTL of anti-MSV immunized F₁ hybrids reacted against tumor cells of both parental strains, suggesting that two different subsets of CTL exist in MSV immunized F₁ mice. One of these subsets reacts with an H-2d modified antigen and one with an H-2b modified antigen. Blocking experiments using anti-H-2 or anti-virus-protein-antisera also indicated that the antigen structure may involve both an H-2 molecule and a viral glycoprotein, gp 69/71. A determinant role for the H-2 region in the immune reaction against tumor induced by type-C oncornaviruses is hypothesized. (6 refs.)

- 77-1019 The Regional Lymph Node in Cancer. Relationship of Nodal Histologic Findings to Cytotoxicity and Immunity.** (Eng.) Fisher, E. R. (Inst. Pathology, Shadyside Hosp., 5230 Centre Ave., Pittsburgh, PA 15232) Fisher, B.; Saffer, E. *Arch Pathol Lab Med* 101(3): 152-155; 1977.

The nodal histologic findings in mice following the amputation of a tumor-bearing limb and two synchronous or asynchronous tumor foci were evaluated. All mice were inbred C₃HeB/FeJ females between 8 and 12 wk old. A spontaneous C₃H mammary carcinoma and an MCA sarcoma produced by the sc injection of methylcholanthrene were used. Nodes near a tumor in the left hind limb exhibited a significantly greater number of pyroninophilic cells in the perifollicular and paracortical areas than in the nonregional nodes after 1 wk. The pyroninophilic cells possessed the features of large lymphocytes and immunoblasts. The degree of nodal

pyroninophilia appeared to increase progressively from 1 to 6 wk after tumor implantation. Epitrochlear lymph nodes from non-tumor-bearing control mice demonstrated significantly greater degrees of sinus histiocytosis than the popliteal or inguinal members. Nodes near a tumor in the hind limb (T₁), in the presence of a synchronously placed second tumor (t₂) in the right foreleg, exhibited a similar degree of pyroninophilia to that in nodes from animals bearing only a single tumor for the same 2-wk period. The asynchronous implantation of a second C₃H tumor (t₂) in the right foreleg 2 wk after the first (T₁) significantly reduced the degree of pyroninophilia in the nodes near both tumors in the synchronous situation. The degree of lymph follicle formation was increased in both nodal sites when a second tumor was asynchronously implanted. When the second asynchronous tumor (t₂) was of the MCA type, the nodes near it, as well as T₁, showed pyroninophilia similar to that in nodes near a solitary tumor focus. Nodes near a tumor-bearing limb studied 4 wk after its amputation demonstrated degrees of pyroninophilia and sinus histiocytosis similar to those observed in the nodes of mice after amputation of a non-tumor-bearing limb. However, lymph follicle formation was greater in nodes near the amputated tumor-bearing limb than in those from the amputation controls. The pyroninophilic elements, with respect to immunoblasts, may be more closely related to cytotoxicity than to tumor immunity per se. (5 refs.)

- 77-1020 Suppressor Cells in Tumor Bearing Mice and Rats.** (Eng.) Kirchner, H. (German Cancer Research Center, Dept. Virology, Im Neuenheimer Feld 280, 69 Heidelberg, W. Germany) Glaser, M.; Holden, H. T.; Fernbach, B. R.; Herberman, R. B. *Biomedicine [Express]* 24(16): 371-374; 1976.

In this study of suppressor cells in tumor-bearing animals, a primary Moloney murine sarcoma virus (MSV)-induced tumor system in C57BL/6 mice was used. The reactivity of spleen cells from tumor-bearing mice to phytohemagglutinin (PHA) was significantly depressed compared with spleen cells from normal mice. The depression was max at the time of max tumor size (14 days after virus inoculation). The depressed PHA reactivity in MSV spleen cell cultures was shown to be caused by suppressor cells. MSV spleen cells consistently suppressed the reactivity of normal spleen cells to PHA when cocultivated in mixture experiments. The suppressor cells in MSV spleen cell populations had to be viable, but they were resistant to x-radiation. The same pattern of results was obtained when reactivity to concanavalin A was tested. B cell stimulation by endotoxin was also significantly depressed at the time of max tumor growth. This depressed reactivity also was caused by suppressor cells. Evidence was obtained that the specific immune reactivity of MSV spleen cells against mitomycin C-treated tumor cells in the mixed lymphocyte-tumor cell interaction was also inhibited by suppressor cells. In the primary MSV tumor system, the peak of primary specific cytotoxicity in a short-term chromium release assay was coincident with the peak of suppressor cell

activity. In vitro removal of the suppressor cells with mitogen reactivity did not enhance cytotoxicity. The suppressor cells were without effect on the effector phase of specific cellular cytotoxicity. Irradiated and anti- θ serum-treated spleen cells from MSV tumor-bearing mice both had a significant suppressive effect on the in vitro secondary cytotoxic response of spleen cells immune to MSV. Similar suppressor cells may play a significant role in the general immunosuppression of tumor-bearing hosts and in their inability to reject the tumor effectively. (23 refs.)

77-1021 Characterization of Suppressor Cells in Mice Bearing Syngeneic Mastocytoma. (Eng.) Takei, F. (Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia, Canada V6T 1W5) Levy, J. G.; Kilburn, D. G. *J Immunol* 118(2): 412-417; 1977.

Suppressor cells from syngeneic P815 mastocytoma-bearing DBA/2 mice, which inhibit the in vitro generation of specific cytotoxicity against P815 tumor cells mediated by T lymphocytes, are characterized. They are found in the spleens and thymuses of mice bearing progressively growing P815 tumors. T lymphocytes appear to be involved in the suppression, since the effectiveness of the suppressor cells was unimpaired by treatment with anti-mouse Ig serum and complement, or by carbonyl iron and magnet. However, the suppressive activity was abrogated by anti-BA θ serum and complement. Furthermore, suppressor cells were specific to the tumor. Both cytotoxic killer cells and suppressor cells in P815 tumor-bearing mice appear to belong to the T lymphocyte population. Attempts were made to differentiate one population from the other by Ficoll-Hypaque density cell separation. Killer cells were enriched in the heavier fraction, suppressor cells in the light fraction. However, it is possible that they are different stages of cell differentiation of the same T-lymphocyte subpopulation. (21 refs.)

77-1022 Growth Regulation and Suppression of Metastasis in the Congenitally Athymic Nude Mouse. (Eng.) Stiles, C. D.; Roberts, P. E.; Saier, M. H.; Sato, G. In: *Modern Trends in Human Leukemia II. Biological, Immunological, Therapeutical and Virological Aspects*. Neth, R.; Gallo, R. C.; Mannweiler, K.; Moloney, W. C., eds. (Munich: F. Lehmanns Verlag): pp. 185-194; 1976.

The capacity of congenitally athymic nude mice to support and to control the growth of various heterologous tissue culture cell lines was investigated. The animals were injected with $1-2 \times 10^6$ viable cells sc into the scapular region. Embryonic cell strains (Balb/c, HFL-Johnson, HFL 2) never grew tumors in nude mice, whereas all established cell lines of neoplastic origin (RPMI 2650, C6, B-16, HeLa, BRL-4143) were tumorigenic. Established cell lines derived from explants of nonneoplastic animal tissue (Balb/c 3T3, MDCK, BRL, 31A, 3T6) were not tumorigenic, except for the 3T6 line.

Every line of SV40 transformed mouse cells tested (SVT2, 56-1, T, XIII, PY 3T3, A-9) was tumorigenic. None of five lines of SV40 transformed human cells (VA2-8-aza-G, RBSV3, RBSV-1A, LNSV, WI-L2) produced tumors even though three human lines derived from authentic neoplasms and a line of human lymphocytes from a nonleukemic patient were tumorigenic. The failure of particular cell lines to grow tumors in nude mice indicated an authentic response to host mediated growth regulatory signals. Experiments involving the determination of several in vitro growth parameters (serum growth requirement, ability to grow on top of stationary phase mouse monolayer cultures, ability to grow in methocel suspension, and the cell saturation density) for various cell lines revealed that there is no absolute correlation between any of these in vitro growth parameters and the tumorigenic potential in immunologically tolerant hosts. A direct test of the metastatic potential of a highly metastatic subclone of B-16 mouse melanoma (#2) cells (10^6 cells injected sc into the scapular region) confirmed that metastasis is suppressed in athymic nude mice. The observation corroborates the experiments with similar B-16 melanoma cells, which revealed that low numbers of lymphocytes from tumor bearing animals actually promote metastasis in thymectomized x-irradiated C57 mice. The capacity of tumor cells to grow in suspension, invade surrounding tissues, and develop secondary metastases appears to require a thymus-dependent function. (9 refs.)

77-1023 Immunity to Lymphoid Tumors Induced in Syngeneic Mice by Immunization with Mitomycin C-treated Cells. (Eng.) Benjamini, E. (Dept. Medical Microbiology, Sch. Medicine, Univ. California, Davis, CA 95616) Fong, S.; Erickson, C.; Leung, C. Y.; Rennick, D.; Scibienski, R. J. *J Immunol* 118(2): 685-693; 1977.

The prophylactic and therapeutic immunogenicity of mitomycin C-treated (MCT) tumor cell lines EL-4 and S49A was assessed. Immunization with MCT syngeneic lymphoid tumor cells induced a very strong antitumor immunoprophylaxis in syngeneic mice. Animals immunized with MCT cells exhibited high levels of cell-mediated cytotoxicity, but they did not produce antibodies; thus, no effective immunotherapy was produced by these vaccines. Transplantation sc or ip of 10^5 viable cells of EL-4 or S49A resulted in rapid demise of the mice; fewer cells caused high mortality over longer times. Three weekly injections of 10^6 MCT tumor cells immunized the animal to as many as 10^8 viable EL-4 cells and 10^5 S49A cells. The immunization was shown to be specific to the cell line. (21 refs.)

77-1024 Thiopental Inhibition of Tumor Immunity. (Eng.) Duncan, P. G. (Dept. Anesthesiology, Health Sciences Center, 700 William Ave., Winnipeg, Manitoba, Canada) Cullen, B. F.; Ray-Keil, L. *Anesthesiology* 46(2): 97-101; 1977.

The effect of thiopental on the ability of WBC to kill ^{51}Cr labeled YACC-1 tumor cells was investigated in vitro using tumor cells obtained from syngeneic A/JAX white mice with immune WBC from allogeneic C57/black mice. Thiopental, in concentrations found in the blood after induction of anesthesia, reversibly inhibited cell-mediated cytotoxicity in a dose- and time-related manner. Halothane and thiopental had additive inhibitory effects on cell-mediated cytotoxicity. Thiopental inhibition of tumor cell killing was greatest when the lytic activity of the effector or killer cells (PEC) in control culture was less than maximal. Inhibitions of cytotoxicity following 4 hr exposure to thiopental ranged from 8.6% at $2.8 \times 10^{-5}\text{M}$ to 38.1% at $8.5 \times 10^{-5}\text{M}$ and were statistically significant above $2.8 \times 10^{-5}\text{M}$. Thiopental inhibition was also related to the duration of exposure. Spontaneous release and max release of ^{51}Cr were not affected. There was no alteration in culture pH or effector cell viability and the effectiveness of killing was not modified by sodium carbonate alone. It appears that thiopental inhibits target-cell killing by an effect on immune PEC. (29 refs.)

- 77-1025 Enhancement of Tumor Growth by Dinitrochlorobenzene (DNCB).** (Eng.) Jessup, J. M. (Surgery Branch, NCI, Bethesda, MD) Riggs, C.; Cohen, M. H. *Surg Forum* 27: 136-137; 1976.

The ability of a single, non-cross-reacting chemical, dinitrochlorobenzene (DNCB), to enhance tumor growth was evaluated. Two mg of DNCB or the g-equivalent, 2.67 mg of sodium dinitrobenzenesulfonate (DNBS), were dissolved in 0.1 ml of dimethyl sulfoxide (DMSO) and injected sc into one flank of 2-mo-old Balb/c or nude mice. Control mice were either injected with 0.1 ml DMSO or left untreated. Ten days later, all mice were inoculated with 10^6 cells of the syngeneic radiation-induced lymphoma (RL male 1) sc in the opposite flank. Because untreated Balb/c mice bearing 10^6 RL male cells die between 30 and 45 days after tumor inoculation, the number of survivors was determined 50 days after tumor transplantation. The survival of athymic nude mice was determined 25 days after tumor inoculation, since untreated nude mice die sooner after tumor cell implantation. To test the role of lymphoid cells in causing tumor enhancement, splenic lymphocytes were harvested from 10-day DNCB-sensitized or normal Balb/c mice; 10^6 spleen cells were then admixed with 10^6 lymphoma cells and injected sc into Balb/c recipients. There was significantly poorer survival in the DNCB-pretreated Balb/c mice (33/166) than in either the DMSO-pretreated (32/98) or the untreated (49/162) groups. In contrast to the experiments in normal Balb/c mice, the nude mice pretreated with DNCB had significantly more survivors 25 days after tumor inoculation (17/20) than did the untreated group (4/18). To determine if metabolic products of halogenated nitrobenzenes could also enhance tumor growth, normal Balb/c mice were injected with DNBS. The survival of the DNBS-pretreated group (26/47) was significantly improved over that of untreated controls (18/62). To

show that lymphoid cells were mediating the DNCB-induced tumor enhancement, spleen cells were harvested from DNCB-pretreated or normal mice, admixed with the lymphoma cells, and injected into Balb/c mice. When tumor areas were determined 21 days after tumor inoculation, the group receiving DNCB-pretreated spleen cells had larger tumors (2.67 cm^2) than the group receiving normal spleen cells (1.65 cm^2). DNCB thus enhances the growth of subsequently injected lymphoma cells. (3 refs.)

- 77-1026 Some Effects of Oral Administration of BCG on Immune Responses in Cancer Patients.** (Eng.) Lewis, M. G.; Jerry, L. M.; Rowden, G.; Phillips, T. M.; Shibata, H.; Capek, A. In: *BCG in Cancer Immunotherapy*. Lamoureux, G.; Turcotte, R.; Portelance, V., eds. (New York: Grune & Stratton, Inc.): pp. 339-358; 1976.

The effects of oral BCG on nonspecific and tumor-directed immunological responses were assessed in 66 patients (59 with malignant melanoma and 7 with other malignancies). Sera from 53 normal individuals were also tested. The only significant changes in nonspecific immune parameters were elevated levels of serum IgA in 9/12 patients and decreased peripheral blood monocyte counts in 7/14 patients. In tests for antitumor immune responses, the patients showed rises in lymphocytotoxicity but little or no rise in anticytoplasmic antibody response. The effect on anti-F(ab'); antibody was a fall in 6/13 individuals and a rise in only 4/15. In patients given oral BCG following an initial rise and fall of antitumor immunity after autoimmunization with irradiated tumor cells id, both autologous antimembrane antibodies and lymphocytotoxicity were seen, but there was little effect on anticytoplasmic antibodies. Xenogenic antisera raised in a chimpanzee, a goat, and several rabbits to melanoma extracts showed cross-reactivity with BCG. The findings suggest the possibility that BCG given po might produce tolerance to the cross-reactive melanoma cytoplasmic antigens and allow a more selective antimembrane immune response. (42 refs.)

- 77-1027 Influence of Whole Body Irradiation on BCG Contact Suppression of a Rat Sarcoma and Tumour-Specific Immunity.** (Eng.) Pimm, M. V. (Cancer Res. Campaign Labs., Univ. Nottingham, Univ. Park, Nottingham NG7 2RD, England) *Br J Cancer* 34(2): 199-202; 1976.

The effect of whole-body irradiation BCG contact suppression was assessed. Sarcoma Mc7 was induced by the sc injection of 3-methylcholanthrene and maintained by sc passage in syngeneic female rats. Rats were exposed to 450 rads (whole-body γ -irradiation) from a ^{60}Co source at the rate of 7 rads/min, 24 hr before use. Normal or whole-body-irradiated rats were inoculated sc with a mixture of 5×10^5 to 10^6 tumor cells prepared from solid tissue or harvested from in vitro culture and 200-500 μg wet wt of BCG organisms. With both normal and irradiated animals, admixture

with BCG prevented tumor development in almost all rats, tumor cells alone, whether from solid in vivo growths or in vitro culture. The influence of whole-body irradiation on the ability of animals rejecting mixed cell + BCG inocula to control the growth of a simultaneous challenge with tumor cells alone was examined. In the first test, only 2/7 normal animals rejecting mixed inocula of 10^6 sarcoma Mc7 cells and $100 \mu\text{g}$ BCG failed to reject a simultaneous challenge inoculum of 10^6 cells alone on the other side of the body. However, tumors grew out at the challenge site in all seven rats receiving whole-body irradiation, even though the animals all rejected the mixed inoculum of tumor cells + BCG. In two further tests, although the challenge inoculum of cells alone grew out in only 4/10 normal animals rejecting cells + BCG on the other side of the body, this immunotherapeutic effect was totally abolished in preirradiated animals, with challenge inocula growing out in all 13 rats. In the final test, using Mc7 cells harvested from in vitro culture, 4/5 normal animals rejecting mixed inocula of tumor cells + BCG rejected a contralateral challenge of 10^6 tissue culture-derived cells, but this therapeutic response was abrogated in 5/6 preirradiated rats. These studies show that whole-body irradiation 24 hr before and does not abrogate the local suppressive effect of BCG injected in admixture with sarcoma Mc7 cells. (7 refs.)

77-1028 Study of Cellular Immunology in Malignant and Benign Monoclonal Gammopathies. (Fre.) Gasparotto, G. (Istituto di Medicina Clinica dell'Universita, Via Giustiniani 2, I-35100 Padova, Italy) Semenzato, G.; Tosato, F.; Cazzaro, G.; Amadori, G. *Schweiz Med Wochenschr* 106(50): 1823-1825; 1976.

The functional situation of circulating lymphocytes was studied in 25 patients with myeloma and 15 with benign paraproteinemia. The lymphocytes were studied by incorporation of ^3H -thymidine after phytohemagglutinin stimulation. E rosette formation and immunoglobulin bearing cells were studied. Myeloma patients had a significant reduction in the incorporation of labeled thymidine. The reduction was not significant in benign monoclonal gammopathies. The different in vitro blastic responses of the two groups of patients in vitro demonstrated the differences in their immunocompetent systems. (8 refs.)

77-1029 Modulation of Agglutinability by Alteration of the Surface Topography in Mouse Ascites Tumor Cells. (Eng.) Oppenheimer, S. B. (Dept. Biology, California State Univ., Northridge, CA 91330) Bales, B. L.; Brennenman, G.; Knapp, L.; Lesin, E. S.; Neri, A.; Pollock, J. G. *Exp Cell Res* 105(2): 291-300; 1977.

A study is presented of the concanavalin A (Con A)-mediated agglutination of mouse sarcoma 180 ascites tumor cells in the presence or absence of cytochalasin B (CB) using a quantita-

tive electronic particle counter assay. The test materials were added to 0.2-ml aliquots of suspensions containing 1.5×10^6 cells/ml. CB ($20 \mu\text{g}/\text{ml}$) substantially increased agglutination of S-180 cells with $10 \mu\text{g}/\text{ml}$ Con A by 60% after 20 min. Scanning and transmission electron microscopy showed that CB causes the formation of large, broad, cell surface ruffles and the loss of narrow projections that appear to be microvilli. Studies with fluorescent Con A suggest that lectin receptor sites concentrate on these ruffles, which seem to mediate the increased agglutinability in this system. Electron spin resonance studies suggest that the lipid "fluidity" in these cells is not altered by CB. The gross cell surface topography favoring high agglutinability is concluded to be one displaying broad ruffles, not numerous narrow projections. (24 refs.)

77-1030 Adherent Cells in Tumor Immunity. (Eng.) Burk, M. W. (Dept. Surgery, Univ. Minnesota, Minneapolis, MN 55455) Burk, K. R.; Yu, S.; McKhann, C. F. *Cell Immunol* 30(1): 43-53; 1977.

The role of adherent cells in tumor immunity and their interaction with tumor antigen and lymphocytes were examined. Lymph node and spleen cells from C3H mice bearing large methylcholanthrene-induced tumors ($> 1 \text{ cm}$ in diameter) were cultivated alone or with mitomycin-blocked cells of the same tumor. The intact lymph node cells did not undergo increased DNA synthesis when cultured in the presence of tumor cells. If the same lymph node cells were first depleted of adherent cells, the remaining nonadherent lymphocytes would undergo stimulation. This same phenomenon was not seen with spleen cells. This indicates that the lymph node cells were maximally stimulated in vivo and incapable of further stimulation by the same tumor cells in vitro. This suggests that the adherent cells provide tumor antigen in native or processed form that is capable of continuously stimulating immune lymphocytes to undergo DNA synthesis and proliferation. Alternatively, adherent cells from tumor-bearing animals may in some way be activated and capable of nonspecifically stimulating T cells without involving tumor antigen. (11 refs.)

77-1031 Immune Competence and Immunosuppressive Factors in Splenectomized Tumor-Bearing Mice. (Eng.) Whitney, R. B. (Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia, Canada V6T 1W5) Pope, B. L.; Levy, J. G. *Cell Immunol* 28(1): 15-21; 1977.

Immune competence and immunosuppressive factors were evaluated in splenectomized tumor-bearing female DBA/2J mice. A methylcholanthrene-induced sarcoma syngeneic to

these mice was utilized. Three weeks prior to tumor cell inoculation, splenectomy had no effect on tumor growth. Tumor appearance and growth were the same in sham-treated and splenectomized mice. There was no significant difference between the groups at any time. Both concanavalin A (Con A) and lipopolysaccharide (LPS) responses of spleen cells were significantly decreased in nonsplenectomized mice. However, there was no difference between lymph node Con A responses in normal and tumor-bearing mice with or without spleen. There was also no difference between the controls and splenectomized tumor-bearing lymph node Con A responses. The LPS responses of both types of tumor bearers were enhanced. Unstimulated spleen and lymph node cells of tumor bearers incorporated more ^3H -thymidine than did normal cells. Tumor-specific immunity was completely lacking in the spleen and lymph nodes of sham-splenectomized normal and large-tumor-bearing mice. Splenectomized normal or large-tumor-bearing mice also had no demonstrable antitumor activity in their lymph nodes. Spleen cells from sham-operated tumor bearers inhibited both the LPS and Con A responses of normal spleen or lymph node cells. Lymph node cells of sham-treated tumor bearers were not suppressive, and splenectomy did not promote the development of suppressor cells in tumor-bearing lymph nodes. Serum from tumor-bearing and normal mice was collected and separated on Sephadex G-150 into a high (immunoglobulin-containing) and a low-molecular-wt fraction. Highly suppressive activity was present in the former fraction of both sham-treated and splenectomized tumor bearers. No suppressive activity was detected in the low molecular wt fraction of each. It may be that the nonspecific serum inhibitor and splenic suppressor cells do not directly influence tumor growth but are important in that they reduce immunologic competence toward general infection. (25 refs.)

77-1032 A Multiple Parameter Comparison of Immunocompetence and Tumor Resistance in Aged BALB/c Mice. (Eng.) Perkins, E. H. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) *Mech Ageing Dev* 6(1): 15-24; 1977.

Immunocompetence and tumor resistance in aged BALB/c mice are compared. The resistance of old (25 mo) and young adult (3 mo) mice was evaluated by injecting (ip) 10^4 and 10^5 or 10^5 and 10^6 P815 mastocytoma cells. The 30-day cumulative mortality showed a significant difference in resistance of young and old animals to the ascites form of this tumor. In 25-mo-old mice, tumor cells multiplied rapidly. Ascites was pronounced 1 wk after inoculation of 10^5 cells, and a majority of the animals died 1-2 wk postinoculation. A corresponding sigmoid mortality curve that was delayed 3-4 days and resulted in approx 90% mortality was observed with 10^4 cells. Animals died within 3 wk of tumor inoculation. However, injection of 10^5 and 10^6 tumor cells produced only 18% and 27% mortality in 3-mo-old mice. Ascites was delayed and less pronounced, and regressed in many animals. Deaths did not occur until the beginning of the third wk and, as in the case

of the old mice, animals that survived 3 wk survived indefinitely. A mean spleen index of 3.3 was seen with spleen cells from young adult (3- to 5-mo-old) BALB/c donors. The mean spleen index decreased to 2.1 with spleen cells from 21- to 22-mo-old mice and to 1.6 with 24-mo-old donors. As judged by ^3H -thymidine incorporation in the spleen, spleen cells of young mice were $2.3\times$ more active than spleen cells of 24-mo-old mice. The lymphoproliferative response of the draining popliteal lymph node from 24-mo-old animals was significantly less than that from 3-mo-old animals 7 days after foot-pad inoculation of tumor cells. When the in vitro phytohemagglutinin response of spleen cells from 3-mo-old animals was compared with that from 24-mo-old animals, the difference in activity was significant. On the basis of differences in the amount of ^3H -thymidine incorporated, spleen cells from young adult mice were $5.5\times$ more active than the same number of cells from old animals. The humoral immune response of old mice, as measured by the number of direct plaque forming cells generated in the spleen in situ, was both delayed and decreased. At 4 days, the response of old mice was almost $100\times$ less. At 5 and 6 days, this difference was less pronounced. When the peak plaque forming cell responses of young adult and old animals were compared, the response of young adult mice was $7\times$ greater. There may be a decreased ability of noncycling T-cells to be released to a functional cycling state. (25 refs.)

77-1033 Heterotransplantation of Retinoblastoma into the Athymic "Nude" Mouse. (Eng.) Gallie, B. L. (Dept. Ophthalmology, Wellesley Hosp., 160 Wellesley St. E., Toronto, Ontario, M4Y 1J3) Albert, D. M.; Wong, J. J.; Buyukmihci, N.; Puliafito, C. A. *Invest Ophthalmol Visua Sci* 16(3): 256-259; 1977.

Fresh retinoblastoma cells and Y-79 cells were implanted (1) in a single-cell suspension in RPMI 1640 medium with 1% penicillin and streptomycin, (2) into the anterior chamber of the eye and sc into nude mice (nu/nu); and (3) into the anterior chamber of the eye of their heterozygote (nu/+) littermates. The anterior injection contained approx 6,000 cells; the sc one 10^6 - 10^7 cells. Twelve of the 13 fresh retinoblastoma transplants into the nu/nu mice filled the anterior chamber and spread into the vitreous humor and retina. Histologically the tumor remained similar to the original. All tumors failed to grow sc in untreated nu/nu mice. When treated with cyclophosphamide (300 mg/kg) prior to injection, 3/4 mice grew sc tumors as large as the whole animal; however, these tumors did not destroy or invade normal tissue. The Y-79 cell injections resulted in invasions of the orbit, optic nerve, and brain. Sc implantation of these cells produced large tumors. Retinoblastoma heterotransplanted into the anterior chamber of nu/+ immunologically normal mice produced little growth. In vitro, explants and single cell suspensions survived for only 1 or 2 wk; cells harvested from mouse eyes also survived only a short time. (9 refs.)

77-1034 Effect of Early Thymectomy on Growth of Transplanted Mammary Gland Tumors Arising in C3Hf Mice. (Eng.) Videlets, I. Y. (Inst. Cytology and Genetics, Acad. Sciences USSR, Siberian Branch, Novosibirsk, USSR) *Exp Biol Med* 81(6): 896-898; 1976.

The influence of early thymectomy on the growth of transplanted mammary gland tumors arising in C3Hf mice is studied. Mice of the C3H/He strain or (C3H/He x C57BL)F₁ hybrids were used as the MTV-S+ animals and C3Hf or 57BL x C3H/He)F₁ hybrids as the MTV-S- group. Three tumors arising spontaneously in a colony of C3Hf mice were utilized: OMZhF-2, OMZhF-3, and OMZhF-4. The MTV-S+ and MTV-S- mice were inoculated simultaneously with 0.2 ml of a 10% suspension of tumor cells sc in the dorsal region. No significant differences were found between the av wt of tumor in the MTV-S+ and MTV-S- recipients, but after transplantation of the OMZhF-2 tumor a significantly higher percentage of transplanted tumors was observed in the C3Hf mice than in the C3H/He mice. In the case of the other two tumors, no significant differences were found in the percentage of successfully transplanted tumors or in the duration of the av latent period between the MTV-S+ or S- recipients. Infection of the recipients at an early age with Bittner virus did not lead to more rapid growth of the transplanted tumors arising in the MTV-S- mice. Experiments were carried out in C3H/He and C3Hf mice. The experimental animals were thymectomized on day 6 after birth. At the age of 3 mo, the mice were inoculated with 0.2 ml of a 10% suspension of OMZhF-2 or OMZhF-4 tumor cells sc in the dorsal region. Early thymectomy on C3H/He (MTV-S+) mice had no inhibitory action on the rate of growth of the transplanted mammary gland tumors arising in MTV-S- mice of the C3Hf strain. In C3Hf(S-) mice, early thymectomy likewise did not affect the rate of growth of the transplanted S- tumor of the C3Hf mice. The results indicate that the more rapid growth of the tumor in the MTV-S+ mice and its delay after early thymectomy are connected with the immunological response to virus-induced antigens. (11 refs.)

77-1035 Hybrid Effect in Natural Cell-Mediated Cytotoxicity of SV40-Transformed Fibroblasts by Rat Spleen Cells. (Eng.) Williams, R. M. (Moliney Farber Cancer Inst., Div. Tumor Immunology, Harvard Medical Sch., Peter Bent Brigham Hosp., Boston, MA 02115) Leifer, J.; Moore, M. J. *Transplantation* 23(3): 283-286; 1977.

Natural cell-mediated cytotoxicity by normal Brown Norway (BN) rat spleen cells was demonstrated against four clones of simian virus 40 (SV40)-transformed BN fibroblasts. However, spleen cells from age- and sex-matched F₁ hybrids [(WF x X)F₁ and (DA x BX)F₁] tested against the same target cells showed superior cell-mediated lysis compared with BN spleen cells. Data that show this hybrid superiority are given. These results suggest that the hybrid effect for natural cell-mediated cytotoxicity may be useful for studying the genetic control of natural immune reactivity against transformed cells. (22 refs.)

77-1036 Immunity to Virus-Free Syngeneic Tumor Cell Transplantation in the BALB/c Mouse After Immunization with Homologous Tumor Cells Infected with Type C Virus. (Eng.) Al-Ghazzouli, I. K. (Microbiological Associates, Building 1, Walkersville, MD 21793) Donahoe, R. M.; Huang, K. Y.; Sass, B.; Peters, R. L.; Kelloff, G. J. *J Immunol* 117(6): 2239-2248; 1976.

The immunity to virus-free syngeneic tumor cell transplantation in the BALB/c mouse following immunization with homologous tumor cells infected with type-C virus is evaluated. To determine the tumorigenic potential of WM-7, graded doses from 5×10^3 to 10^7 cells were inoculated sc into six groups, 10 mice/group of syngeneic BALB/cCr mice. The percentage of tumor incidence and av latent period were noted to be dose dependent. All of the recipients that received the highest doses (10^7 and 5×10^6 WM-7 cells) developed tumors with an av latent period of 15-25 days, whereas 5 of 10 and 3 of 10 developed tumors at the lowest doses (1×10^3 and 5×10^4 , respectively) with an av latent period of 40-79 days. The tumorigenic potential of WM-7 tumor cells with or without Rauscher murine leukemia virus (R-MuLV) infection was compared. Uninfected WM-7 cells grew well when injected sc in BALB/cCr mice, and in all cases in which tumors appeared, death resulted from tumor growth. However, R-WM-7 cells, after being maintained in tissue culture for four population doublings and transplanted even with as many as 10^7 cells, produced neither death nor growing tumors either initially or during the 5 mo of observation. Immunization of adult mice with x-irradiated R-WM-7 or WM-7 tumor cells did not confer any significant protection against challenge with a lethal dose of the viable WM-7 cells. Animals in which virus-positive tumors regressed were significantly resistant to challenge with live R-MuLV as well as uninfected tumor cell lines. Spleen cells from mice whose virus-infected tumors regressed were cytotoxic to homologous infected and uninfected tumor cells; they were also cytotoxic to uninfected tumor cell lines syngeneic to BALB/c mice. Type-C virus infection of syngeneic tumor cells results in their acquiring strong transplantation antigens. (32 refs.)

77-1037 Development of Transplanted Experimental Leukemia NK/Ly under the Influence of Antierythropoietic Immune Serum. (Rus.) Fedorov, N. A. (Lab. Pathophysiology, Central Inst. Hematology Blood Transfusion USSR Ministry Public Health, Moscow, USSR) Reshchikov, V. P.; Fertukova, N. M.; Gudim, V. I.; Moskaleva, G. P.; Khokhlova, M. P.; Vinogradova, G. F.; Zaretsky, I. I. *Probl Gematol Pereliv Krovi* 21(10): 37-40; 1976.

The action of antierythropoietic immune serum on hemopoiesis in experimental leukemia was investigated. Inhibition of leukemia development was noted during the course of administration of the antierythropoietic immune serum. It is suggested that inhibition of the erythropoietin activity is important in the action mechanism of the antierythropoietic serum. (2 refs.)

- 77-1038 Genetic Association of the Humoral and Cellular Immune Responses of Rats to Moloney Sarcomas.** (Eng.) Veit, B. C. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Jones, J.; Miller, G. A.; Feldman, J. D. *Int J Cancer* 19(1): 97-106; 1977.

The genetic basis for immune response to tumor-associated antigens expressed on rat Moloney sarcoma cells was examined. BN, Le, LBN (Le × BN), and parent-to-LBN backcross rats received 5×10^7 BM2 tumor cells sc. Tumors grew at similar rates in BN, Le, and LBN rats to day 8. BN tumors continued to grow progressively, resulting in nearly complete mortality by 50 days. Le rats rejected the tumors after day 8 and were tumor-free by day 16. (Le × LBN) backcrosses were comparable in rejection behavior to Le. All hosts had three to six times the cytotoxic antibody activity as the Le-LBN group. Using MST tumor cells, BN and LBN sera had higher amounts of anti-p30 (the major viral core antigen) than Le and Le × LBN sera. Le rats were also less susceptible to sc injections of Moloney virus. Max splenic cell-mediated cytotoxicity (CMC) after BM2 injection was 34%-54% on day 10 in the Le-LBN system relative to 17%-24% on day 8 in the BN-LBN system. Lymph node cell peaks in Le-LBN were also considerably higher. The CMC responses in the Le-LBN system were directed against tumor-associated antigens rather than the histocompatibility antigens of tumor cells. Humoral and cellular responses to Moloney sarcoma virus imply a genetic linkage, rather than association with the major AgB histocompatibility locus, and genetic regulation (possibly by Ir genes) of effector T-cell populations. (21 refs.)

- 77-1039 Macrophages in Regressing and Progressing Moloney Sarcomas.** (Eng.) Russell, S. W.; Doe, W. f.; Cochrane, C. G. In: *The Macrophage in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 199-206; 1976.

Regressing and progressing Moloney sarcomas were examined histologically and after disaggregation with enzymes in an investigation of the role of tumor macrophages in vivo. The Moloney sarcoma was induced by im injection of cultured MSC cells into adult mice. Regressing tumors were uniformly infiltrated by inflammatory cells, but the host inflammatory response was restricted to the peripheries of progressing sarcomas. The tumors were disaggregated using a papain/collagenase/DNase mixture that yielded up to 6.5×10^8 viable cells/g tumor and DNA recoveries as high as 50%-60%. The percentage of macrophages in regressing tumors after 11-13 days was two to three times that in progressing sarcomas. The total number of macrophages per tumor, however, was the same (1.3×10^8) for each type. When the difference in size between the two types of tumor is considered, the number of macrophages per gram is five times greater in the smaller, regressing sarcomas than in the progressing neoplasms. Coincident with the appearance of inflammatory infiltrates, mitotic activity in regressing tumors all but ceased. Analysis of both regressing and progressing tumors con-

firmed the intimate association of cytostasis with the presence of mononuclear cells: mitotic activity was suppressed throughout regressing neoplasms but was diminished only at the edges of progressing sarcomas. The centers of progressing sarcomas, which were devoid of inflammatory elements, exhibited many mitotic figures. Macrophages obtained from disaggregated tumors suppressed the uptake of ^3H -thymidine into two unrelated types of neoplastic cells in vitro. This result suggests interference with tumor cell replication. Suppression appears to be nonspecific because a neoplastic cell type (simian virus 40) other than the one used to induce tumors was affected. The implication of these data is that macrophages help to mediate the regression of Moloney sarcomas. (16 refs.)

- 77-1040 Differences in Surface Membrane Charge Normal and Leukemic Leukocytes Shown by Polycation Migration Inhibition.** (Eng.) Moroson, M. (New York Medical Coll., New York, NY 10029) Choi, K. I.; Rotman, M.; DaCosta, M. *IRCS Med Sci: Cancer* 5(2): 1977.

The surface charge on the membranes of leukemic (chronic myelocytic: CML) WBCs was studied by observing the effect of polycations on their migrating ability. The migration of normal WBC was inhibited 20%-23% by $2 \mu\text{g}/\text{ml}$ of polylysine; that of leukemic WBC was enhanced 13%. Migration of leukemic WBC was scarcely inhibited by polypropyleneimine; normal WBC were inhibited 19%-31%. It appears that these two polycations can discriminate between normal and CML leukocytes. (4 refs.)

See also

- * (Rev.): 77-0658, 77-0660, 77-0680, 77-0682, 77-0685, 77-0686, 77-0687, 77-0688, 77-0689, 77-0691, 77-0692, 77-0693, 77-0694, 77-0695, 77-0697, 77-0698, 77-0699, 77-0700, 77-0701, 77-0703, 77-0704, 77-0705, 77-0706, 77-0707, 77-0709, 77-0710, 77-0711, 77-0712, 77-0713, 77-0724, 77-0725, 77-0732, 77-0736, 77-0740, 77-0744, 77-0750.
- * (Chem.): 77-0803, 77-0817.
- * (Phys.): 77-0856, 77-0860.
- * (Viral): 77-0890, 77-0891, 77-0897, 77-0899, 77-0914, 77-0918, 77-0919, 77-0921, 77-0933, 77-0939, 77-0944, 77-0949, 77-0952, 77-0958, 77-0965, 77-0968, 77-0969, 77-0970, 77-0975, 77-0983, 77-0984, 77-0986, 77-0988.
- * (Path.): 77-1051, 77-1056, 77-1057, 77-1085, 77-1110, 77-1119, 77-1124, 77-1125, 77-1127, 77-1151.
- * (Epid.-Biom.): 77-1151, 77-1152.

PATHOGENESIS

7-1041 **Progesterone Receptor in Cystosarcoma Phyllodes.** (Eng.) Rao, B. R. (Section Cancer Biology, Mallinckrodt Inst. Radiology, Washington Univ. Sch. Medicine, St. Louis, MO 63110) Meyers, J. S. *Arch Surg* 112: 620-622; 1977.

A specific receptor for progesterone was found in a cystosarcoma phyllodes (an infrequent breast tumor involving both epithelial and stromal elements) from a 69-yr-old woman, as determined by charcoal adsorption and sucrose gradient analysis of the tumor cytosol. Similar assays for estrogen receptors were negative. On the morning following mastectomy, serum estradiol 17β was 250 pg/ml; 9 mo after surgery, it was 10 pg/ml. The high serum estradiol- 17β level on the first day after surgery may reflect an elevation of circulating estrogen in response to operative stress. The site of the progesterone receptors in the cystosarcoma could not be determined, but the fact that this tumor contained few ducts, < 1% of its volume, suggests that they were located in the stromal epithelium. The presence of the progesterone receptors indicates that some cystosarcomas are hormonally regulated and that they may be responsive to therapeutic hormonal manipulation. (16 refs.)

7-1042 **T and B Lymphocytes in Breast Cancer (Letter to Editor).** (Eng.) Teasdale, C. (Univ. Dept. Surgery, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales) Thatcher, J.; Whitehead, R. H.; Chare, M.; Hughes, L. E. *Lancet* 1(8010): 543-544; 1977.

The T, B and total lymphocyte counts were studied in 100 breast cancer patients (59 ± 13 yr old), 22 younger (49 ± 9 yr) patients with benign breast disease and 31 healthy women (58 ± 12 yr). The patients were studied before treatment. Total lymphocytes and per cent T-cells were higher in both control groups than in the breast cancer patients ($p < 0.05$). However, Stage III cancer patients compared separately to controls did not differ significantly in T-cells or lymphocytes. These normal values in Stage III patients are not explained. (4 refs.)

7-1043 **Endometrial Stromatosis of the Uterus.** (Eng.) Hart, W. R. (Dept. Pathology, Univ. Michigan Medical Sch., 1335 E. Catherine St., Ann Arbor, MI 48109) Bonessi, M. *Obstet Gynecol* 49(4): 393-403; 1977.

A clinical and pathologic study is presented of 9 patients with endometrial stromatosis of the uterus, including one with the

circumscribed variant. All patients were white; the age range was 18-69 yr at diagnosis. Of eight with known parity, two were nulliparous. Known presenting symptoms in eight patients included abnormal vaginal bleeding in six, abdominal pain in one and back pain with urinary frequency in one. Among seven subjected to pelvic examination, six had a known palpable mass or enlarged uterus; polypoid pieces of tumor were found in the cervical os of the other patient. One patient with circumscribed stromatosis and four with invasive stromatosis were alive and free of tumor 1.2 to 15.6 yr after initial surgery. Four other patients with invasive stromatosis died with tumor 3.8 to 9.4 yr after surgery. The lack of high mitotic activity and cytologic anaplasia and the relatively indolent behavior of stromatosis justify its separation from the more aggressive endometrial stromal sarcomas. (19 refs.)

77-1044 **The Pathogenesis of Ovarian Inclusion Cysts and Cystomas.** (Eng.) Radisavljevic, S. V. (Western Pennsylvania Hosp., Pittsburgh, 15224) *Obstet Gynecol* 49(4): 424-429; 1977.

Several thousand sections from 1,000 ovaries were examined to determine the pathogenesis of germinal inclusion cysts and ovarian cystomas. Usually the oophorectomy was carried out with hysterectomy for various gynecologic-urologic indications or else with salpingectomy for ectopic pregnancy. The patients ranged from 19 to 75 yr old, with most being premenopausal. Reconstructions and dynamic interpretations of the ovarian morphology indicated that the lesions are almost always initiated by the mechanisms of ovulation, both normal and abnormal, and the consequent alterations of the ovarian surface. The spread of surface epithelium into naturally occurring ovarian cavities, ie, follicles, corpora lutea, and corpora albicantia in all their modifications, constitutes one of several mechanisms for cyst production. Even when all the conditions necessary for their formation are present, inclusion cysts do not invariably form. The behavior of ovarian cysts appears to depend on the type of epithelium and type of stroma. The interactions of epithelium and stroma are not the same in various combinations, and patients may present a variety of changes. Hormonal, inflammatory, and circulatory influences may also affect the behavior of the cyst. (20 refs.)

77-1045 **Rectal Metastasis of an Ovarian Tumor 26 Years after Surgery.** (Fre.) Bodin, F. (Service de Gastro-Enterologie A, Hopital Saint-Antoine, 184, rue du

Faubourg Saint-Antoine, 75012 Paris, France) Dyan, S.; Licht, H.; Conte-Marti, J.; Crottogini, J. J. *Nouv Presse Med* 6(6): 466; 1977.

Metastases of ovarian cystadenocarcinomas to the digestive tract are rare, and a rectal site of a metastasis, as reported in this case of a 78-yr-old woman, is unique. The polylobulated, ulcerated tumor, 3 cm in diameter, was located on the anterior surface of the rectum. The tumor was removed endoscopically in two operative sessions. Histologically, it proved to be a cystadenocarcinoma identical to that found in an ovary 26 yr earlier when the patient underwent hysterectomy and bilateral ovariectomy. The patient was observed for 18 mo after surgery, and there was no evidence of recurrence. (4 refs.)

77-1046 Ovarian Thecal Metaplasia in Adrenal Glands. (Eng.) Fidler, W. J. (Dept. Pathology, Univ. Michigan, Ann Arbor, MI 48109) *Am J Clin Pathol* 67(4): 318-323; 1977.

A retrospective study was conducted to define the prevalence, morphology, and significance of ovarian thecal metaplasia of the adrenal glands. Histologic sections prepared from 552 adrenal glands surgically removed from 276 women, primarily because of metastatic cancer of the breast, were examined. Nodules of ovarian thecal metaplasia were found in the adrenal glands from 14 patients. Thirteen of the women were postmenopausal, and one had ovarian stromal hyperplasia. The lesions were frequently multiple and bilateral and were almost always located just beneath the adrenal capsule. Metastatic carcinoma of the breast was present in only two cases. Neither hyperplasia nor adenomas were observed in the adrenals. Only 1/14 women had functioning ovaries at the time the lesion was found. These lesions probably represent metaplasia of embryologically competent cells that become transformed into ovarian tissue under the influence of unopposed pituitary gonadotropin during or after menopause. It is not known whether these nodules have functional significance in the human female. (25 refs.)

77-1047 Theca-like Reactions in the Stroma of Tumors of the Ciliated Epithelium of the Ovaries. (Rus.) Torgushina, N. S. (Dept. Pathological Anatomy, S. M. Kirov Gorki Medical Inst., Gorki, USSR) Sumina, T. V. *Arkhl Patol* 38(11): 45-49; 1976.

A theca-like reaction was studied in 283 celio-epithelial tumors of the ovaries from postmenopausal women. There were 50 simple cystadenomas, 28 proliferating cystadenomas and 205 malignant tumors, which had developed from the celio-epithelial cystadenoma. Histochemical reactions similar to

those in the theca cells of normal ovaries (presence of cholesteryl esterase, glucose-6-phosphate dehydrogenase, and lactate dehydrogenase, which are necessary for the biosynthesis of the steroid hormones) were observed in 70.6% of the malignant tumors of the ovaries and in 57.1% of the proliferating celio-epithelial cystadenomas, while in the simple cystadenomas the theca-like reaction was absent. (22 refs.)

77-1048 Vaginal Adenosis: Colposcopic and Histological Aspects. Report of 17 Cases, 11 Spontaneous Cases and 6 Cases Developing after Estrogen Administration During Fetal Life. (Fre.) Henry-Suchet, J. (Service de Gynecologie-Obstetrique, Centre Hospitalier, 141, Grand Rue, 92310 Sevres, France) Charpentier, E.; Seneze, J.; Bruix, J. *Rev Fr Gynecol* 72(2): 127-140; 1977.

Literature on vaginal adenosis is reviewed and 17 cases are reported, 11 from 1,000 cases in a file of gynecological patients and 6 from among 16 girls or women exposed to diethylstilbestrol (DES) in utero. The incidence of adenosis in DES-exposed women varies from 30% to 91% in the literature, but histological criteria and methods of diagnosis differ. Vaginal adenosis was benign in the 17 cases reported, but the lesions were much more pronounced in the DES-exposed subjects. Endocervical type glandular epithelium was typical of the adenosis histopathology; however, the endometrial type was of the endometrioid type in one non-DES-exposed woman. Glycogen was irregular when it was present, but it was more often absent. In 5/11 subjects exposed to DES, a congenital lesion such as an imperforated hymen or a double uterus was associated with the adenosis. Extensive vaginal adenosis rarely undergoes malignant transformation. More frequently, it leads to a refractory chronic vaginitis with dyspareunia, and early treatment with progesterone and/or destruction of the lesion with electrocoagulation is recommended. (29 refs.)

77-1049 Microglandular Hyperplasia in Vaginal Adenosis Associated with Oral Contraceptives and Prenatal Diethylstilbestrol Exposure. (Eng.) Robboy, S. (Dept. Pathology, Massachusetts General Hosp., Boston, MA 02114) Welch, W. R. *Obstet Gynecol* 49(4): 430-437; 1977.

The microscopic features of biopsy specimens from eight patients with microglandular hyperplasia arising in vaginal adenosis are described. The patients ranged in age from 17 yr; five were known to have taken oral contraceptives; one was pregnant when the lesion was discovered, and five had a history of intrauterine exposure to diethylstilbestrol (DES). The lesion involved both the vagina and cervix in five patients.

and was confined to the vagina in three. It is emphasized that estrogen-progesterone combination agents can give rise to vaginal microglandular hyperplasia, and this should be considered before a diagnosis of clear cell adenocarcinoma is considered. The development of microglandular hyperplasia within the DES-exposed population appears to be a rare phenomenon, despite the relative frequency of vaginal adenosis. However, these eight cases suggest that microglandular hyperplasia should be considered in the differential diagnosis of clear cell adenoma of the vagina or cervix in young women of reproductive age, particularly those with a history of concurrent administration of oral contraceptives. (14 refs.)

7-1050 Benign Liver Tumors in Patients Taking Oral Contraceptives. (Eng.) Turney, W. H. (1925 N 5th St., Waco, TX 76707) Shipp, R. F.; Bellegie, N. J. *Tex Med* 73: 75-80; 1977.

The spontaneous rupture of a benign liver tumor with accompanying hemoperitoneum and shock in a patient who had taken oral contraceptives (Ortho-Novum, 2 mg) for 7 yr is reported. A laparotomy revealed a 15-20 cm tumor and an acutely bleeding 12-15 cm rent in the anterior surface of the tumor. Hemorrhage was controlled by ligation of the common hepatic artery at its proximal portion after conservative measures were unsuccessful. This treatment was used as opposed to tumor resection because of the young woman's condition and the location and large size of the tumor. She was well 6 mo after surgery at which time liver function test results were essentially normal. Follow-up liver scans showed that the filling defect in the liver was decreasing in size. The most recent liver scan showed no sign of tumor. Hepatic artery ligation is suggested as an emergency measure to control bleeding rather than hepatic resection. Hepatic resection is suggested when it can be done easily since these benign tumors may rupture spontaneously. A correlation between the use of oral contraceptives and benign tumors of the liver (20 selected cases are listed) is hypothesized. (13 refs.)

7-1051 Viral Hepatitis and Hepatocellular Carcinoma. (Eng.) Ohta, Y. In: *Hepatocellular Carcinoma*. Okuda, K.; Peters, R. L., eds. (New York: John Wiley and Sons, Inc.): pp. 73-81; 1976.

From 1958-1974, 83 patients (15 women, 68 men) with hepatocellular carcinoma (HCC) were hospitalized at the Okayama University Hospital. Most male patients were between the fifth and the seventh decades, but the age of female patients varied widely. Diagnosis was established by autopsy in 46, by peritoneoscopy and liver biopsy in 16, by surgical

biopsy in 5, and clinically, with the aid of liver scans and serum α -fetoprotein, in 16. Of the 67 histologically verified cases, 52 (77.6%) developed HCC superimposed on cirrhosis. A history of viral hepatitis was elicited from 19 patients, all men, and family clustering of chronic liver diseases was a feature of 6. The interval from confirmed acute viral hepatitis to the diagnosis of HCC was 6-20 yr (av 12.8 yr). In patients with unconfirmed acute viral hepatitis, the interval was 4.5-16 yr (av 9.5 yr). The interval from the clinical diagnosis of liver cirrhosis to HCC was 5-15 yr (av 8 yr). According to immune adherence hemagglutination, the rate of positive hepatitis B (HB) surface antigen was 60% in patients developing HCC with a previous history of viral hepatitis and 61.5% in patients with HCC who had no history of viral hepatitis. The positive rate of HB surface antigen in serum was high in patients with HCC. The geographical frequency of HCC patients paralleled the frequency of viral HB. The clustering of liver cirrhosis and HCC in families supports a hypothesis of viral hepatitis causing the development of HCC. (35 refs.)

77-1052 Angiosarcoma of the Liver and Portal Sclerosis in Vinyl Chloride Workers. Report of Two Cases. (Fre.) Bonneton, G. (Service de Chirurgie Vasculaire, C.H.U. de Grenoble, F 38700 La Tronche, France) Champetier, J.; Fournet, J.; Guidicelli, H.; Legrand, J.; Dupre, A.; Hostein, M.; Marty, F.; Pahn, M. *Nouv Presse Med* 6(9): 735-742; 1977.

A 63-yr-old man developed an angiosarcoma of the liver after 12 yr occupational exposure to polyvinyl chloride. He entered the hospital with acute abdominal pain and hypochromic anemia. Hepatosplenomegaly and ascites were evident clinically and confirmed by endoscopic and arteriographic studies. Hepatic scintigraphy showed a multilacunar area near the margin of the right lobe. Laparotomy revealed abdominal hemorrhage and a large, hemorrhagic cyst on the liver. Hepatectomy and splenectomy were performed with immediate satisfactory results; however, rupture of the esophageal varices as a result of portal hypertension led to fatal hemorrhage on the 16th postoperative day. In addition to angiosarcoma of the right lobe of the liver, areas of infarct and intrahepatocytic biliary retention were observed in the left lobe at autopsy. In the second case, the worker developed portal fibrosis and collagenous sclerosis of the liver after more than 20 yr exposure to polyvinyl chloride. A splenectomy was performed in 1968 for splenomegaly; the spleen proved to be inflamed and fibrous without evidence of malignancy. Five years later, the patient was hospitalized for melena and found to have hypochromic anemia, moderate hepatomegaly, and significant esophageal varices. At surgery, the liver appeared to have disseminated micronodules, but no tumor was detected. The portal vein was fibrosed and a mesenterico-vena cava anastomosis was performed with excellent postoperative results. (13 refs.)

- 77-1053 Malignant Tumors of the Extrahepatic Bile Ducts.** (Eng.) Andersson, A. (Centralsjukhuset, Kristianstad, Dept. Surgery, Univ. Umea, Sweden) Bergdahl, L.; van der Linden, W. *Surgery* 81(2): 198-202; 1977.

A series of 76 patients (35 women and 41 men; 24-87 yr, mean 68 yr) who were treated between 1952 and 1973 for carcinoma of the extrahepatic bile ducts were reviewed. Jaundice was seen in 71, upper abdominal pain in 42, loss of wt in 27, hepatomegaly in 30, and a palpable tumor mass in 11. The lesion was located in the hepatic ducts in 23, in the cystic and common ducts in 24, and in the papilla of Vater in 23. Metastases were more commonly associated with carcinoma in the ducts than in the papilla of Vater; this was probably due to the early onset of jaundice in the latter and thus early treatment. Gallstones were found in 22 patients; 11 others had undergone earlier cholecystectomy for gallstone disease. Only 68/76 patients underwent surgery. The mean survival for cancer of the papilla of Vater was 11.5 mo, that for cancer of the hepatic ducts was 11.7 mo, and that for cancer in the common and cystic ducts was 6.18 mo. The disappointing operative results are in accordance with those reported by others. Radical surgery should be considered in every case of carcinoma of the extrahepatic bile ducts. (13 refs.)

- 77-1054 Hormone Blood Levels in Patients with Prostatic Carcinoma and Their Relation to the Type of Carcinoma Growth Differentiation.** (Eng.) Bartsch, W. (Dept. Clinical Chemistry, 2nd Medical Clinic, Univ. Hamburg, Martinistrasse 52, D-2000 Hamburg, W. Germany) Steins, P.; Becker, H. *Eur Urol* 3(1): 47-52; 1977.

The blood levels of hormones in prostatic carcinoma patients were studied. The subjects included 29 patients with recently diagnosed cancer before they received medication or surgery, 20 hospitalized control patients, and a second control group of 18 nonhospitalized men. A positive pigeon crop sac assay was found in 50% of the patients with prostatic carcinoma, but only in 20% of the hospitalized and 11% of the ambulant controls. Histological examination of biopsied prostatic material revealed four types of tumor: highly and poorly differentiated adenocarcinomas, cribriform carcinomas, and carcinomas with solid growth. One form of differentiated carcinoma was established in 57% of the cases, whereas 43% showed two forms of differentiation. Carcinomas with cribriform and/or solid growth demonstrated increased pigeon crop sac activity and higher testosterone, 5 α -dihydrotestosterone, and estrone levels in plasma than tumors without such growth. The luteinizing hormone values were lower in the carcinoma group than in both control groups, but follicle-stimulating hormone values revealed no statistical differences from group to group. It is not known whether the hormones induce the type of tumor growth or whether the type of tumor is responsible for the hormonal environment. (38 refs.)

- 77-1055 Prostatic Caruncle: A Urethral Papillary Tumor Derived from Prolapse of the Prostatic Duct.** (Eng.) Hara, S. (Urologic Service, Sanshinkai Ha Hosp., 1-8 Daihakucho, Higashiku, Fukuoka 813, Japan) *Urol* 117(3): 303-305; 1977.

Tiny papillary tumors of the prostatic urethra in and around the verumontanum were demonstrated by urethroscopy in 10 patients (average, 42 yr) who presented with hematuria. A frequent clinical sign was post-ejaculatory hematuria. Histopathologic study revealed evagination of prostatic glandular tissue with polypoid, papillary and angiectatic patterns in varying degrees. These lesions may be called prostatic caruncles because of their close similarity to female urethral caruncles. The mild inflammatory changes noted in these patients were considered secondary reactions to the local circulatory disturbance and erosion. Two patients had recurrence of tumor. Follow-up was at least 3 yr for 19 patients. (13 refs.)

- 77-1056 The Ileal Loop: A Novel Approach to Study Lymphoid Depletion Mediated by Urine.** (Eng.) Tapper, D. (Dept. Surgery, Univ. California, San Francisco Sch. Medicine, San Francisco, CA) *Surg Forum* 27: 129-133; 1976.

Intestinal segments exposed to urine were investigated and compared to intestine no longer exposed to urine because of diversion clinically and experimentally. Since 1952, 10 ileal loop diversions have been performed at the Children's Hospital Medical Center, Boston, and 16 of these patients eventually underwent diversion. Segments of intestine were observed histologically at three stages in the clinical course: creation of the ileal loop, reestablishment of urinary continuity, and excision of a defunctionalized loop of intestine. A ileal loop was created in 11 dogs by anastomosing the right ureter to a segment of terminal ileum 8 cm from the ileocecal valve. Two wk later, urine residual was measured in the ileal loop, and serum creatinine was determined. After 4-12 wk a right nephroureterectomy was performed that included the prox 25% of the proximal portion of the ileal loop and contained the ureteroileal anastomosis. This represented intestine exposed to urine. Later (4-8 wk), the remaining defunctionalized segment of the loop was excised. This represented intestine no longer exposed to urine. In four control dogs, a defunctionalized intestinal loop was created. Peyer's patches in the human terminal ileum included mature lymphoid elements coalescing to form follicles with healthy germinal centers. After exposure to urine, the follicles were smaller and depleted of mature, active cells. The layer of lymphoid elements usually noted beneath the villi contained only scanty lymphoid cells. When the urine was removed, the lymphoid cells recovered their plump, healthy appearance and the layer above the lamina propria was repopulated with lymphoid elements. In the intestinal segments of all the ar

is, urine exposure resulted in a significant depletion of lymphoid elements from the Peyer's patches and from beneath the intestinal villi in the intestine. There was an associated hypertrophy of the lymph nodes in the ileal loop mesentery. When the intestine was no longer exposed to urine, there was prompt regeneration and reappearance of the lymphoid elements. The hyperplastic lymph nodes in the ileal mesentery regressed when urine exposure was removed. These studies demonstrate that exposure of small intestine to urine causes significant lymphoid depletion and that subsequent exclusion of urine permits lymphocyte repopulation. (15 refs.)

77-1057 Increased Incidence of Malignancy in Uremic Patients and Its Significance to Transplantation. (Eng.) Matas, A. J. (Dept. Surgery, Univ. Minnesota Medical Sch., Minneapolis, MN 55455) Simmons, R. L.; Billstrand, C. M.; Buselmeier, T. J.; Johnson, T. L.; Starzl, J. S. *Transplant Proc* 9(1): 1137-1140; 1977.

Charts of all patients submitted to the transplant or dialysis service for evaluation of end-stage renal failure were examined. Twenty-one patients developed 22 de novo malignancies while uremic. The mean age of the patients was 45 yr (range 21-70 yr). The average duration of uremia prior to tumor diagnosis was 39 mo (range 6-120 mo). Polycystic kidney disease was responsible for renal failure in six patients. There were three neoplasms of the thyroid, breast, kidney, and skin, one of the bladder, and one each of uterus, lymphoproliferative system, pancreas (insulinoma), pancreas (adenocarcinoma), lung, stomach, bile duct, and brain. Three patients died as a result of their tumors or their tumors combined with other systemic problems. Ten patients received renal transplants after treatment of their respective tumors. In 3/10, the tumors were diagnosed while the patients were still in the hospital immediately following renal transplantation. All three tumors were resected. In seven cases, the tumor was resected, and each patient was observed for tumor recurrence while on dialysis. No patient developed evidence of metastases or recurrence following transplantation (6 mo-6 yr). Nine of the 10 patients are alive and well 8 mo to 4 yr post-transplantation. (11 refs.)

77-1058 A Rare Association of Hamartomas of the Kidney, Renal Insufficiency, Bourneville's Disease, and Arterial Hypertension. (Fre.) Aubert, J. (Service de Néphrologie, Hôtel-Dieu, 8600 Poitiers, France) Casamayou, J. Larregue, M. *J Urol Nephrol (Paris)* 83(3): 195-202; 1977.

A case is reported of Bourneville's disease (tuberous sclerosis), renal insufficiency, arterial hypertension, and bilateral

hamartomas of the kidneys in a 52-yr-old man. The disease was evident in the numerous adenomas of the nose and chin, including a large pedunculated tumor on the left nostril. Multiple lesions covered the trunk, and x-rays of the skull showed multiple calcifications. Bourneville's disease could be traced in his family for three generations. Urography showed greatly enlarged kidneys, and these studies together with echography suggested polycystosis. Scintigraphy indicated diminished renal activity in both kidneys. Surgery was not performed. (15 refs.)

77-1059 Tumors of the Uropoietic Tract in the Area of Endemic Nephropathy. (Cro.) Mircic, L. (Medical Center, 15300 Loznica, Yugoslavia) *Libri Oncol* 4(3/4): 185-188; 1975.

Malignant tumors of the uropoietic tract in the area in which endemic nephropathy also appears are discussed in terms of several cases. Over a 3-yr period, the number of patients with these tumors constantly rose, to a total of 651; over half of all patients were farmers. Based on this high frequency in an area with endemic nephropathy, a correlation between the two has been established. (7 refs.)

77-1060 Development and Characterization of Cell Lines of Normal Mouse Bladder Epithelial Cells and 2-Acetylaminofluorene-induced Urothelial Carcinoma Cells Grown in Monolayer Tissue Culture. (Eng.) Berky, J. J. (Microbiology and Immunology Div., Natl. Center Toxicological Res., Jefferson, AR 72079) Zolotor, L. *In Vitro* 13(2): 63-75; 1977.

Methods of obtaining mouse urinary bladder epithelium and maintaining it in long-term monolayer culture were developed, and cultures from tissues of normal mice were compared with cells from 2-acetylaminofluorene (2-AAF)-induced carcinomas of mouse urinary bladders. One epithelial-like line of normal cells has been maintained in culture through 40 passages over 15 mo. Cell lines of normal bladder epithelium were mononucleated, sheet-forming cells with a modal chromosome number of 40. Bladder epithelial carcinoma cells were polynucleated, relatively fast-growing, and able to grow in soft agar; they demonstrated a higher cloning efficiency than normal cells and formed tumors when injected into syngeneic hosts. The tumorigenic line had a colchicine-arrested metaphase modal number of 80, which may be indicative of a transformed line stabilized in the tetraploid state. The striking differences between the normal epithelial cell morphology and that of the tumorous bladder line have allowed easy microscopy differentiation with phase optics, by means of scanning electron microscopy and the use of stained preparations. (31 refs.)

- 77-1061 Colonic Tumors after Ureterosigmoidostomy for Exstrophy of the Bladder. Anatomic-Clinical Study of Two Cases.** (Fre.) Potet, F. (Service d'Anatomie et de Cytologie Pathologiques, Hôpital Beaujon, F 92110 Clichy, France) Weiss, A. M.; Soullard, J.; Cendron, J. *Gastroenterol Clin Biol* 1(1): 59-65; 1977.

A 32-yr-old man and a 34-yr-old woman developed cystic polyp tumors, one with adenocarcinomatous changes, at the site of ureterosigmoidostomies performed for exstrophy of the bladder 25 yr previously. A nephrectomy had been performed on the man for recurrent infection 2 yr prior to the discovery of a voluminous polyp at the right ureteral orifice. A second tumor was discovered and removed at the left ureteral orifice, 3 mo after excision of the first tumor. In the case of the woman, cystic, inflamed polyps 1 and 6 cm in diameter were discovered simultaneously. Local excision of the tumors was followed by reimplantation of the ureters. Macroscopically, the tumors were polylobulated polyps attached by a sessile or pediculated base. On cross-section, large mucus-filled cysts were noted. Epithelium persisted on the surface of the polyps, but it was infiltrated with inflammatory cells. In the case of the man, the first tumor removed showed a malignant proliferation of cells on the surface. A review of 25 literature cases of tumors developing at the site of ureterosigmoidostomies for exstrophy of the bladder revealed that most were anaplastic or adenocarcinomas; the remainder were juvenile-type polyps. (25 refs.)

- 77-1062 Hexosamine-containing Macromolecules in Human Colon Carcinomas.** (Eng.) Terho, T. (Dept. Physiology, Univ. Turku, Turku, Finland) Laitio, M. *Scand J Gastroenterol* 12(1): 7-15; 1977.

A histochemical, morphological and biochemical study was made of normal, transitional, and carcinoma areas of five colons resected for carcinoma. The transitional area contained a larger amount of nonsulfated acid mucin than normal mucosa, which contained mainly sulfated mucin. The hexosamine-containing macromolecules studied were: (1) acid glycosaminoglycans (AC); (2) high-molecular-wt glycopeptides (HMW-G); and (3) low-molecular-wt glycopeptides (LMW-G). The carcinoma areas contained an av of 859 μ g total hexosamines/g wet wt, compared to 422 μ g/g in the normal areas. AC were identified as hyaluronate, heparan sulfate, dermatan sulfate and chondroitin 4-(6)-sulfate. Their concentrations increased from normal to transitional and from transitional to carcinoma areas. HMW-G was composed of fucose, galactose, glucosamine, galactosamine, sialic acid, and variable amounts of sulfate; sulfation degree was highest in normal areas. LMW-G consisted of about a half of the total hexosamine-containing substances. The mean concentration of the saline-insoluble fraction of the LMW-G in transitional areas was 166 μ g/g wet wt, and in carcinoma areas, 166 μ g compared to 95 μ g/g in normal areas. (33 refs.)

- 77-1063 Squamous Carcinoma of the Stomach after Luetetic Linitis Plastica.** (Eng.) Vaughan, W. I. (Johns Hopkins Hosp., 601 N. Broadway, Baltimore, MD 21205) Straus, F. H.; Paloyan, D. *Gastroenterology* 72(5): 945-948; 1977.

A case history is presented of a 49-yr-old woman with long standing inflammatory linitis plastica caused by congenital syphilis. The patient presented with typical obstructive complaints, postprandial abdominal pain, vomiting without nausea, and wt loss. The long-standing syphilis, achlorhydria and classical roentgenographs were accepted as diagnostic of inflammatory linitis attributable to syphilis when a biopsy could not be obtained. Her course was complicated by a multifactorial anemia and progressive inanition. Gastric washings contained atypical squamous cells almost 3 yr before the diagnosis of carcinoma, and focal squamous metaplasia was found throughout the stomach. The most likely pathologic sequence of events was chronic syphilitic gastritis progressing to inflammatory linitis plastica and squamous metaplasia which then underwent malignant transformation. There are several other reports of squamous metaplasia of the stomach in patients with inflammatory linitis plastica. The coexistence of carcinoma and inflammatory linitis plastica is also mentioned, but these cases have not been well-documented. Neither a history of syphilis nor positive serology is unusual common in squamous carcinoma of the stomach, suggesting that this patient may illustrate only one pathophysiologic mechanism for the development of this tumor. (21 refs.)

- 77-1064 Three Cases of Gastric Cancer Recurrence More than Ten Years after the Initial Operation.** (Jpn.) Hoshino, H. (First Dept. Surgery, Tokyo Medical and Dental Univ., Tokyo, Japan) Hoshi, K.; Murakami, T.; Kataoka, T. *Stomach Intest* 12(1): 41-46; 1977.

The case reports of three patients with gastric cancer that recurred > 10 yr after the initial operation are presented. The first patient was an 81-yr-old woman who had undergone resection 16 yr previously for type IIb early gastric cancer. The recurrent cancer extended from the gastroduodenal stump to the esophageal mucosa. The resected specimen was classified as a stump-type recurrence. The second patient was a 49-yr-old woman who had undergone resection for type IIa + IIc early gastric cancer 10 yr previously. The operative specimen from the second resection demonstrated cancerous infiltration on the abdominal esophagus away from the stump. This cancer was considered a nonsimultaneous multiple cancer. The third patient was a 68-yr-old man who had undergone curative resection 15 yr previously for type PA (proper muscle) advanced cancer. This recurrence was also considered a nonsimultaneous multiple cancer. Since recurrence of gastric cancer appears to take a long time, it is suggested that 10-yr survival rates are better than 5-yr ones for estimating the operative cure rate. (12 refs.)

1065 **Four Cases of Gastric Cancer Recurrence More than 10 Years after Gastrectomy.** (Jpn.) Takagi, (Dept. Surgery, Cancer Inst. Hosp., Tokyo, Japan) Adachi, H.; Nakajima, T.; Ohashi, I. *Stom Intest* 12(1): 47-52; 1977.

A study was made of four patients with gastric cancer that recurred > 10 yr after surgical correction. The first patient was a 37-yr-old woman with infiltrative scirrhous adenocarcinoma. Thirteen years after gastrectomy, ovariectomy was performed. She died of pulmonary metastasis 15 yr after the last operation. The second patient was a 42-yr-old woman with infiltrative scirrhous carcinoma who had undergone gastrectomy. She died from peritoneal dissemination 10 yr and 2 mo later. The third patient was a 69-yr-old man who had undergone gastrectomy for a gastric ulcer. After 12 yr and 2 mo, the remnant stomach was excised because of cancer. He died of lung metastasis 6 yr and 2 mo after the second operation. Reexamination of the initially resected stomach indicated early cancer, type IIa+IIc (submucosa). The fourth patient was a 48-yr-old man who had also undergone resection for a gastric ulcer. Reresection was performed 13 yr and 5 mo later because of a cancer in the remnant stomach. Four months later he died of peritoneal dissemination. Reexamination of the initial specimen indicated type IIc+III (mucosa) cancer. The importance of histologic examination of the cardiac end of the initially resected stomach is emphasized. Cancer that recurred after 5 yr was generally in an early stage; recurrence after 10 yr was generally accompanied by peritoneal dissemination. The detection of cancer in the remnant stomach raises the question as to whether it is really recurrence or a nonsynchronous cancer. The differentiation of these types is discussed. (9 refs.)

1066 **Adenocarcinoma in Regional Enteritis of the Small Intestine.** (Eng.) Hoffman, J. P. (Dept. Surgery, Virginia Mason Hosp., Seattle, WA) Taft, D. A.; Wheelis, R. F.; Walker, J. H. *Arch Surg* 112: 606-611; 1977.

Forty-nine cases from the literature and 2 new cases of small bowel adenocarcinoma in patients with regional enteritis (RE) were analyzed to determine if patients with RE are at increased risk for small bowel adenocarcinoma. These cases (Group A) were compared with a current group (B: 272 cases) of small bowel adenocarcinoma not associated with RE. In group A, the mean age at cancer diagnosis was 46 yr, compared to 64 yr for Group B; more cancers arose in the ileum of Group A patients (75% vs 27%), and diagnosis and cure were less successful. The paucity of preoperatively diagnosed cancers in the Group A patients probably stems from the similarity in clinical and roentgenographic presentation of small bowel adenocarcinoma and recrudescence RE. The delay in diagnosis and therapy is probably the reason for the poor prognosis. An RE patient has a minimum risk of

small bowel adenocarcinoma development that is from 6 to 320 times as great as that of a person of the same age without RE. Since so many of the reported cases occurred in individuals with long-standing disease, it is speculated that risk increases with RE duration, but data to prove this are lacking. (53 refs.)

77-1067 **Villous Tumors of the Duodenum.** (Eng.) Spira, I. A. (Dept. Surgery, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10003) Wolff, W. I. *Am J Gastroenterol* 67(1): 63-68; 1977.

A new case of villous tumor of the duodenum is presented, and the 41 previously reported cases are reviewed. In the new case (59-yr-old man), a villous tumor that was excised from the second portion of the duodenum showed no evidence of malignancy in frozen section. Histological examination revealed the typical appearance of villous adenoma at the periphery but the central portion showed evidence of invasive adenocarcinoma. Of the 41 literature cases, 11 were also associated with invasive adenocarcinoma. These were confined to patients over 50 yr of age. Benign villous tumors may be locally excised, but tumors with invasive adenocarcinoma require resection of the duodenum, usually in the form of a pancreaticoduodenectomy. Caution is advised in that the superficial portions of the tumor may appear benign, but deeper portions may contain invasive adenocarcinoma. Patients who have had a local excision of a villous tumor of the duodenum should be followed endoscopically and radiologically at suitable intervals. (34 refs.)

77-1068 **Malignant Acanthosis Nigricans--A Paraneoplastic Syndrome?** (Eng.) Hage, E. (Dept. Pathology, Odense Univ. Hosp., DK-5000 Odense, Denmark) Hage, J. *Acta Dermatovenereol (Stockh)* 57(2): 169-172; 1977.

A case of acanthosis nigricans associated with gastric carcinoma in a 71-yr-old woman is reported. The carcinoma was of the diffuse, infiltrating type. Histochemical and electron microscopic studies of the gastric carcinoma identified many tumor cells as enterochromaffinlike (ECI) cells of the APUD (amine content, precursor uptake, and decarboxylase) series of endocrine cells. The tumor was thereby classed as an APUDoma. The most striking feature of the cells was the numerous secretory granules that almost filled the cytoplasm. Membranes of adjacent secretory granules were in close contact or even fused with one another. Many of the cells were able to secrete polypeptide or amine hormones. It is suggested that in this case functionally transformed tumor ECI cells could produce a substance that activates the dermatosis. Furthermore, this could be a property shared by all cells in the

APUD series of endocrine cells when they become tumor cells. This would explain the various localizations of the malignant tumor in cases of acanthosis nigricans. This would also explain the disappearance of the dermatosis after cancer treatment and its reappearance when cancerous activity resumes. (17 refs.)

- 77-1069 Vasoactive Intestinal Polypeptide and Gastrin-producing Islet Cell Carcinoma.** (Eng.) Judge, D. M. (Dept. Pathology, Baylor Coll. Medicine, Houston, TX 77030) Demers, L. M.; Nahrwold, D. L.; Dickman, P. S.; Petrokubi, R. J.; Trapukdi, S. *Arch Pathol Lab Med* 101(5): 262-265; 1977.

A 61-yr-old woman presented on admission with watery diarrhea, anorexia and wt loss, hypokalemia, hypochlorhydria, and elevated serum gastrin levels. At surgery, a mass was noted in the body of the pancreas with metastases to the liver; the body and tail of the pancreas were excised. Radioimmune assay and immunofluorescence demonstrated both vasoactive intestinal polypeptide (VIP) and gastrin in the surgically removed carcinoma and in a metastatic focus. Electron microscopic examination revealed the presence of two distinct cell types, one containing condensed mitochondria, short segments of narrow cisternae of rough endoplasmic reticulum (RER), and varying numbers of α -type granules, and the other containing open mitochondria, abundant dilated RER, and varying numbers of dense granules. These secretory granules had characteristics of both hormones, with each type being confined to different cells. Plasma prostaglandin E levels were also elevated. The patient's course was typical of Verner-Morrison syndrome. This case is unusual because the combination of VIP and gastrin is seldom found in islet cell carcinoma. (12 refs.)

- 77-1070 Adenoma of the Islets of Langerhans in a New-born Infant. Clinical, Endocrinological, and Ultrastructural Observations.** (Fre.) Demarquez, J. L. (Centre de Pathologie neo-natale et de prematurress, Hopital des Enfants, 168, cours de l'Argonne, 33000 Bordeaux, France) Vital, C.; Babin, J. P.; Allain, D.; Bondonny, J. M.; Sautarel, M.; Rancon, F.; Martin, C. *Arch Fr Pediatr* 34(2): 179-191; 1977.

Adenoma of the islets of Langerhans is rare in infants; however, 800 adult cases were reported from 1960 to 1969. In this case, the infant developed convulsions and cyanotic crises on the second day after birth. Gestation had been normal. A severe hypoglycemia did not respond to po glucose, iv corticosteroids, glucagon, and diazoxide. The infant had the appearance of one born to a diabetic mother, but the mother's response to a glucose tolerance test was normal. Radioim-

munoassay of the serum showed an increase in the insulin:glucose ratio, characteristic of an islet cell tumor. Operation revealed a nodule on the isthmus of the pancreas. The nodules and the caudal pancreas were removed, but the infant died on the eight postoperative day from respiratory failure. The insulin concentration in the tumor was much higher than that in the normal pancreatic tissue (1,760 versus 200 $\mu\text{g/g}$). Ultrastructurally, the adenoma differed from those of adults and children reported in the literature in that the cytoplasm of some of the histiocytes showed a heavy concentration of electron dense deposits of collagen fibers. (53 refs.)

- 77-1071 "Somatostatinoma": A Somatostatin-containing Tumor of the Endocrine Pancreas.** (Eng.) Gauda, O. P. (One Joslin Place, Boston, MA 02215) Weir, G. J.; Soeldner, J. S.; Legg, M. A.; Chick, W. L.; Patel, Y. C.; Ebeid, A. M.; Gabbay, K. H.; Reichlin, S. *N Engl J Med* 296(17): 963-967; 1977.

A 46-yr-old woman with a pancreatic tumor containing an extremely high quantity of somatostatin was studied. The patient was first examined because of excessive urination and thirst accompanied by wt loss. Her blood glucose level was 488 mg/deciliter. She was treated with diet, tolbutamide (150 mg/day), and phenformin (50 mg/day). Seven years later the patient was admitted with acute abdominal pain and nausea. Chronic cholecystitis was diagnosed, and a cholecystectomy was performed. A pancreatic mass was discovered at operation and biopsy showed it to be a tumor of endocrine morphology, resembling D cells. The tumor was later completely resected at laparotomy. Before operation there was no evidence of overproduction of insulin or glucagon. Analysis of the tumor revealed 301 nanograms of immunoreactive somatostatin per milligram of tissue. Tumor concentrations of insulin and glucagon were below those in the normal pancreas. Only trace amounts of gastrin and vasoactive intestinal polypeptide were found. Tissue culture studies of the tumor cells showed that they released somatostatin into the culture medium and remained viable for at least 51 days. After resection of the tumor, the patient's glucose level returned to normal. (40 refs.)

- 77-1072 Metastases to the Thyroid Gland: Report of Two Cases.** (Fre.) Froidevaux, A. (Clinique universitaire de chirurgie, Hopital cantonal, Geneve, Switzerland) Megevand, R. *Helv Chir Acta* 44(1/2): 175-185; 1977.

The literature concerning metastases to the thyroid gland plus two case reports are presented. Metastases to the thyroid, usually from carcinomas of the urogenital tract or lung, are considered rare, but incidences as high as 17% of all cancers in general have been reported. In the first case,

4-yr-old woman had multinodular metastases to the thyroid and from a cylindrical cell, nonsecreting adenocarcinoma of the colon excised 5 yr previously. A total thyroidectomy was performed, but the patient died 3 mo later of generalized metastases. The second case, a 41-yr-old woman, underwent left thyroid lobectomy for a single nodule. Histological examination confirmed a metastasis from an adenocarcinoma of the rectum excised 3 yr previously. Pulmonary metastases were also present. The patient had chemotherapy postoperatively. When the thyroid metastasis is part of a generalized dissemination of the original carcinoma, removal of the thyroid gland will not alter the prognosis. (24 refs.)

77-1073 **Electron Microscopy of Clear Cell Thyroid Carcinoma.** (Eng.) Valenta, L. J. (Dept. Medicine, Univ. California Medical Center, 101 City Drive South, Irvine, CA 92668) *Arch Pathol Lab Med* 101(3): 140-144; 1977.

Three cases of clear cell thyroid carcinoma were examined by electron microscopy and biochemical techniques. The accumulation of glycogen caused the clear appearance of cytoplasm. The rough endoplasmic reticulum was poorly developed. Free ribosomes, mostly arranged in polysomes, appeared to be in excess. The Golgi apparatus was hyperplastic. Relatively few dense bodies of lysosomal character were identified. The intracellular accumulation of glycogen may be the result of the selective loss of the peptide portion of thyroglobulin. (17 refs.)

77-1074 **Pituitary Growth Hormone Cell Adenoma with Cytoplasmic Tubular Aggregates in the Capillary Endothelium.** (Eng.) Kovacs, K. (Dept. Pathology, St. Michael's Hosp., 30 Bond St., Toronto, Ontario M5B 1W8, Canada) Horvath, E.; Pritzker, K. P.; Schwartz, M. L. *Acta Neuropathol (Berl)* 37(1): 77-79; 1977.

The presence of cytoplasmic tubular aggregates (CTA) in the capillary endothelium of a sparsely granulated growth hormone cell adenoma was revealed by electron microscopy. The tumor had been surgically removed from a 25-yr-old acromegalic patient. The CTA were located either under the outer nuclear membrane or inside the dilated endoplasmic reticulum, which suggests that they arose from the nucleus and subsequently migrated to the cytoplasm. Further studies must be made to ascertain the nuclear derivation of CTA and to explain of their functional significance and their correlation with various pathogenic states. (26 refs.)

77-1075 **Prevalence and Presentation of Hyperprolactinaemia in Patients with "Functionless" Pituitary Tumours.** (Eng.) Franks, S. (Cobbold Labs., Middlesex Hosp. Medical Sch., London W1N 8AA, England) Nabarro, J. D.; Jacobs, H. S. *Lancet* 1(8015): 778-780; 1977.

Serum-prolactin concentrations were measured by a specific radioimmunoassay in 111 patients (57 women, 18-76 yr old; 54 men, 16-70 yr old) who had radiological enlargement of the pituitary fossa but no evidence of acromegaly, Cushing's syndrome, or Nelson's syndrome. Raised prolactin levels (14-5,000 $\mu\text{g/liter}$) were found in 45/64 patients studied before treatment and in 15/47 postoperative patients. The majority of hyperprolactinemic patients presented with amenorrhea or impotence; reproductive disorders were rare in patients with normal prolactin levels. Galactorrhea was detected in 11 of the hyperprolactinemic patients studied before treatment and in 1 studied after surgery. Recognition of a pituitary tumor as the cause of impotence or amenorrhea was rare at an early stage. In the investigation of patients with amenorrhea or impotence, serum-prolactin should be measured and skull radiology performed if the prolactin level is raised. Prolactin should also be measured in all patients with abnormal pituitary x-rays both before and after pituitary surgery. Persistent reproductive difficulties after hypophysectomy are more often attributable to hyperprolactinemia than to gonadotrophin deficiency, and they may be reversed by secondary treatment with bromocriptine. (17 refs.)

77-1076 **Biological Factors Involved in the Clinical Features and Surgical Management of Cerebellar Hemangioblastomas.** (Eng.) Obrador, S. (Eduardo Dato, 23, Madrid, 10, Spain) *Surg Neurol* 7(2): 79-85; 1977.

The case reports of 65 patients with cerebellar hemangioblastoma and 474 cases from the literature are reviewed in regards to their clinical, biological and surgical aspects. Headaches and cerebellar deficit, both as the result of raised intracranial pressure, appeared in 76 and 10% of the patients, respectively. Papilledema was present in 90%, cerebellar signs in 61-76% and nystagmus in 42-62%. A familial history of vascular tumors in the CNS or other organs was occasionally present. There was an increase in Hb and in the number of RBC with cerebellar hemangioblastomas, between 5 and 31%. These increases are not associated with other signs of hematological diseases and may be the result of a humoral stimulation factor for the production of RBC. Vertebral angiography was the most useful diagnostic procedure. Hemangioblastomas of the cerebellum, or Lindau tumors, have a preferential localization in the cerebellar hemispheres (approx 79%) followed by the vermis (14%) and the floor of the fourth ventricle (8%). The majority of the tumors have a large cystic component (74%). The solid tumors were similar to the nodular portions of the cystic ones. They were general-

ly not invasive and were well delimited from the surrounding nervous tissue. The tumors were composed of endothelial cells forming a fine mesh of blood spaces and channels with stroma cells lying in the intercapillary spaces; they were polygonal in shape and often had a clear and swollen foamy cytoplasm. There were three cell types: the capillary cavernous juvenile, the transitional ones, and the clear cell type. Surgical excision was the best treatment for capillary hemangiomas of the posterior fossa. The cystic, solid or multiple tumors should be considered separately in terms of their mortality, morbidity, and recurrences. The av postoperative mortality of 523 of these cases was 17%; the mortality rate was closely related to the type of tumors. Solid tumors had a worse prognosis than cystic tumors. Those in the floor of the fourth ventricle were correlated with a high mortality rate. There were two types of recurrence: those due to local growth in situ after incomplete removal of the mural-nodule in cystic or solid tumors and those due to new growth of unsuspected multicentric tumors that were not recognized at first operation. Cystic tumors should be radically treated by evacuation of the cyst and total excision of the mural-nodule, and the solid tumor should be radically excised. The mean figures for good long term results were 72% and for morbidity 9%. (44 refs.)

77-1077 Spread of Epidermoid Carcinoma of the Lip Along the Inferior Alveolar Nerve. (Eng.)

Schmidseder, R. (Kieferchirurgischen Universitätsklinik, Augustusplatz 2, D-6500 Mainz, W. Germany) Dick, H. *Oral Surg* 43(4): 517-520; 1977.

An epidermoid carcinoma of the lower lip that spread along the inferior alveolar nerve to the cranium is described. In 1957, carcinoma of the right lower lip was diagnosed in a 63-yr-old man. After radiotherapy with 7,500 rads, the lesion underwent complete regression and healing. In the fall of 1971, a swelling developed at the original site. The recurrent lesion was excised and, histopathologically, was reported to be an infiltrating epidermoid carcinoma with spread into the labial vestibule. In August, 1972, the patient began to complain of severe pain in the right temporal region. Radiographic examination revealed an osteolytic process in the body of the right mandible. On admission in March 1973, the patient had a swelling 15 mm in diameter in the lower right vestibulum oris at the level of the mental foramen. A radiograph demonstrated a large radiolucency in the body of the right mandible, with widening of the mandibular canal. The right mandible was resected from the symphysis to the angle of the mandible. Close inspection of the proximal stump revealed a pencil-thick alveolar nerve that was interpreted as a sign of tumor infiltration. The resection was extended to include the ramus, with disarticulation of the temporomandibular joint. Postradiotherapy, radiographs showed increased widening of the right foramen ovale. The patient died 18 mo after initial admission, without demonstrable evidence of local or metastatic tumor recurrence. This case shows that carcinoma

of the head and neck may spread along nerve pathways. (13 refs.)

77-1078 Paraneoplastic Cushing's Syndrome. Electron Microscopy of Neurosecretory Granules in a Lymph Node Metastasis. (Fre.) Lorey, Y. (Clinique Therapeutique, Hopital de Pontchaillou, F 35011 Rennes, France) Louvet, M.; Lancien, G.; Leverger, J. C.; Allannic, H.; Vivien, P. *Ann Endocrinol (Paris)* 37(6): 473-474; 1976.

A case is reported of a 44-yr-old man with Cushing's syndrome resulting from a mediastinal tumor, probably of thymic origin. Laparotomy and clinical examination failed to reveal an adrenal tumor when the patient demonstrated symptoms of hypercorticism. Biopsy of the retroclavicular lymph nodes, which had become enlarged, showed neurosecretory granules similar to those observed by other researchers in secretory thymomas and other tumors. The patient died 3 yr after radiotherapy for the lymph nodes. A tumor of the mediastinum, probably a thymoma, was seen at autopsy. There were no metastases, but the adrenal glands showed hyperplasia and polymicroadenomas. (3 refs.)

77-1079 Parotid Carcinoma and Posterior Fossa Schwannoma Following Irradiation: Report of a Patient Treated in Infancy for Benign Ear Disease. (Eng.)

Sogg, R. L. (Div. Ophthalmology, Stanford Univ. Medical Center, 300 Pasteur Dr., Palo Alto, CA 94305) Nikoskelainen, E. *JAMA* 237(19): 2098-2100; 1977.

A case history is presented of a 23-yr-old man in whom both a parotid gland carcinoma and a jugular foramen schwannoma developed > 20 yr after radiation for a benign ear disease. The entire deep lobe and most of the superficial lobe of the left parotid gland were excised along with five lymph nodes. The tumor was diagnosed as an undifferentiated carcinoma of the parotid gland. Four months later, a right posterior fossa craniectomy was performed and a large tumor (identified by skull x-ray, computerized tomographic scanning of the brain, and arteriography) arising from the right jugular foramen and looking grossly like a meningioma was dissected from the cerebellum. The neuropathological diagnosis was schwannoma. Pulmonary metastases developed 1 yr later and the patient is under treatment. The location of both tumors strongly supports the hypothesis that they were radiation-induced. (9 refs.)

77-1080 Two Intrathoracic Cancers That were Probably Radioinduced. (Fre.) Hertzog, P. (Hopital Foch,

40, rue Worth, 92150 Suresnes, France) *Rev Fr Mal Respir* 5(3): 339-342; 1977.

thoracic cancer probably caused by radiation is related to two case reports. In the first case, a woman was treated with a total of 8,500 R for Hodgkin's disease of the mediastinum, which had been confirmed by a supraclavicular lymph node biopsy. An esophageal carcinoma developed on cicatricial stenosis of the esophagus 32 yr later. In the second case, a 51-yr-old man developed locally invasive lung cancer 22 yr after irradiation of the thorax for an unconfined bronchial cancer. The dose administered was 5,000 R. In both patients, extensive fibrothorax with cutaneous ulceration developed after the radiotherapy, and this may have led to the subsequent development of malignancy. (15 refs.)

77-1081 Oat-Cell Carcinoma of the Oesophagus: A Recently Recognized Entity. (Eng.) Cook, M. G. (Dept. Pathology, London Hosp., London E1, England) Eusebio, V.; Betts, C. M. *J Clin Pathol* 28(12): 1068-1073; 1976.

In a case of primary oat-cell carcinoma of the esophagus in a 70-yr-old woman is reported. Esophagoscopy demonstrated a stricture in the esophageal mucosa, and biopsy revealed a poorly differentiated squamous carcinoma. Four esophageal lymph nodes contained metastatic deposits. Two of these had an oat-cell pattern, one was squamous, and the fourth contained both oat-cell and squamous carcinoma. The precise histogenetic relationship of the tumor components is not clear but it is suggested that both components could be derived from the same cell with subsequent divergent differentiation along two distinct pathways. (14 refs.)

77-1082 Mucoepidermoid Carcinoma of the Subglottis. An Ultrastructural Study. (Eng.) Tomita, T. (Dept. Pathology, Univ. Kansas Medical Center, Coll. Health Sciences and Hosp., Kansas City, KS 66103) Lotuaco, J.; Talbott, L.; Watanabe, I. *Arch Pathol Lab Med* 101(3): 155-148; 1977.

The light and electron microscopic features of a well-differentiated mucoepidermoid carcinoma of the subglottis of a 7-yr-old man are reported. The tumor consisted of mucous cells, epidermoid cells, and intermediate cells interrupted by thin, fibrous stroma. Mucous cells formed lumina that were lined with amorphous mucin. Abundant tonofilaments, which were dispersed in practically all tumor cell cytoplasm, formed dense aggregates or converged to the numerous desmosomes. The epidermoid cells varied in differentiation. This is the first ultrastructural study of this type of tumor. (5 refs.)

77-1083 Scanning Electron Microscopy in the Study of Lung Cancer. New Technique of Comparative Studies on the Same Lung Cancer Cells by Light Microscopy and Scanning Electron Microscopy. (Eng.) Takenaga, A. (Dept. Lung Cancer, Center for Adult Diseases, Osaka, Japan) Matsuda, M.; Horai, T.; Ikegami, H.; Hattori, S. *Acta Cytol (Baltimore)* 21(1): 90-95; 1977.

The surface structure of a given cell preparation was observed by light microscopy and scanning electron microscopy to improve identification of malignant cells. Cells were obtained by bronchofiberscopy or from pleural effusions. Fixation in glutaraldehyde and osmium and staining by Papanicolaou's method were the procedures of choice. With this technique, differential diagnosis of adenocarcinoma and mesothelial cells from pleural effusions is easily made. Microvilli were seen on adenocarcinoma cells; oat-cell carcinoma cells had a granular surface. (11 refs.)

77-1084 Pulmonary Carcinoma (Jaagsiekte) of Sheep. Ultrastructural Study of Early and Advanced Tumor Lesions. (Eng.) Hod, I. (Hebrew Univ. Jerusalem, Rehovot Campus, 76-100, Israel) Herz, A.; Zimmer, A. *Am J Pathol* 86(3): 545-558; 1977.

Lung carcinoma of sheep (Jaagsiekte) is a bronchiolar-alveolar cell carcinoma. Differences in the ultrastructural patterns of early and advanced lesions of the disease are described. Samples of early tumor foci were obtained from an apparently healthy young sheep from a multiple-case herd, during elective postmortem examination. A-type and C-type viruses were observed in advanced tumors and were absent in early lesions. Numerous microtubules were characteristic in the epithelial tumor cells of the early lesions but were absent in the advanced tumor. In comparison to the early lesions, extensive cytosome production, surfactant secretion, and glycogen accumulation were observed in the advanced tumor. The immune response to the early tumor lesion was restricted to the peribronchiolar lymph aggregates, while in the advanced stages of the disease the systemic immune response was markedly increased. Hyper-7S-immunoglobulinemia is characteristic of the terminal stages of this disease. (22 refs.)

77-1085 The Pulmonary Metastases of Choriocarcinoma. (Eng.) Libshitz, H. I. (Dept. Diagnostic Radiology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030) Baber, C. E.; Hammond, C. B. *Obstet Gynecol* 49(4): 412-416; 1977.

Among 78 patients with choriocarcinoma or other trophoblastic malignancies, 35 had pulmonary metastases; this incidence rate is lower than that of two previous reports but

probably was caused by referral rather than a difference in virulence. Among the 35 with metastases, the typical metastasis with well-defined rounded density was found in 33. The alveolar type of metastasis was found in only two patients. None of the patients showed embolic metastases. In two patients residual nodules were seen which were not viable tumors. Patients with normal human chorionic gonadotropin titers may have persistent nodules in their lungs which are not viable tumors. (8 refs.)

- 77-1086 Paths of Lymphatic Spread of Bronchial Cancer.** (Fre.) Greschuchna, D. (Ruhrlandklinik de l'Institut d'Assurance Sociale de la Province Rhenane, Essen, W. Germany) *Broncho-pneumologie* 26(5): 388-396; 1976.

In a series of 1,921 cases of bronchial cancer treated in the period 1961-1974, mediastinoscopy prior to surgery revealed lymph node metastases in 689 (36%). Reexamination of pathological tissue excised at surgery of 650 of the cases showed only 24 false negatives for procedure. The location of lymph node metastases, as revealed by mediastinoscopy, is related to site and stage of primary pulmonary cancer. Less than one-fourth of Stages I and II cancers had metastasized to the lymph nodes. Lymph node biopsy was more likely to be positive for cancer of the right lung (41%) than for the left (30%); differences in lobe location, superior (36%), middle (47%), and inferior (32%), were less marked. Overall, the lymph node metastases were most likely to be unilateral (53.7%) rather than bilateral (20.8%) or located at the tracheal bifurcation (20.3%). (11 refs.)

- 77-1087 Case Report 17.** (Eng.) Keats, T. E. (Dept. Radiology, Univ. Virginia Hosp. and Medical Coll., Charlottesville, VA 22901) Brower, A. C. *Skeletal Radiol* 1(3): 177-178; 1977.

An 11-yr-old girl was admitted to the hospital for placement of an artificial eye, at which time a left periorbital swelling was noted. Six years previously, she had undergone surgical removal of an embryonal rhabdomyosarcoma of the left orbit, followed by 6,000 rads of radiotherapy to that area. Ultimately, the patient died of widespread metastases from an osteosarcoma of the left orbit, which, it is believed, was radiation-induced. The cause-and-effect relationship between ionizing radiation and the development of osteosarcoma is discussed and reviewed. (7 refs.)

- 77-1088 Dedifferentiation of Low Grade Chondrosarcomas.** (Eng.) McFarland, G. B. (1514 Jefferson Highway, New Orleans, LA 70121) McKinley, L. M.; Reed, R. J. *Clin Orthop* 122: 157-164; 1977.

Four unusual cases of bone tumor are presented in which the lesion initially appeared to be a low-grade, well-differentiated chondrosarcoma. After the tumors had been removed or between the time of the original biopsy and the definitive procedure, however, the histologic appearance had changed dramatically, being replaced by a highly malignant dedifferentiated tumor. The tumors were low-grade chondrosarcomas, with sharp margins bordered by a fibrosarcoma that appeared to be hemangiopericytoma, rhabdomyosarcoma and synovial sarcoma. The average survival was 12 mo (range 5-18 mo). (15 refs.)

- 77-1089 Intraocular Extension of Squamous Cell Carcinoma of the Conjunctiva.** (Eng.) Nicholson D. H. (Bascom Palmer Eye Inst., Univ. Miami Sch. Medicine, 1638 NW 10th Ave., Miami, FL 33136) Herschle J. *Arch Ophthalmol* 95(5): 843-846; 1977.

A case report is presented that illustrates the clinical appearance, temporal evolution, and histopathologic correlates of intraocular invasion by squamous cell carcinoma of the conjunctiva. The patient (a 65-yr-old man) noticed irritation of the eye 4 mo before examination, which revealed an area of peripheral corneal thinning and apparent adhesion of the adjacent atrophic conjunctiva to the sclera at the temporal limbus. The area of the adherent conjunctiva was bounded by a firm, rubbery, elevated, vascular mass. The clinical impression was probable carcinoma-in-situ of the conjunctiva. Histopathologic examination of the resected mass disclosed a moderately well-differentiated squamous cell carcinoma. A few months after operation, a flocculent whitish cellular material, histologically identified as squamous cell carcinoma, was seen in the anterior chamber of the same eye. Intraocular invasion occurs in < 10% of the patients with invasive conjunctival squamous cell carcinoma, and it can clinically simulate intraocular inflammation. However, the biomicroscopic appearance of pearly tumor cell aggregate enmeshed in a whitish flocculent matrix may be distinctive enough to permit clinical differentiation from inflammatory cells in the aqueous humor, and aqueous humor cytologic study provides an easy method for definitive diagnosis. (4 refs.)

- 77-1090 Skin Fibroblasts from a D-Deletion Type Retinoblastoma Patient Are Abnormally X-Ray Sensitive.** (Eng.) Weichselbaum, R. R. (Lab. Radiobiology Dept. Physiology, Sch. Public Health, Harvard Univ. and Joint Center for Radiation Therapy, Harvard Medical Sch. Boston, MA 02115) Nove, J.; Little, J. B. *Nature* 266(5604): 726-727; 1977.

The x-ray sensitivity of skin fibroblasts from three retinoblastoma patients was studied. Two of the patients were twins

with the familial type of the disease accompanied by no gross chromosome abnormalities, and the third patient had a D-deletion-type retinoblastoma. Fibroblasts from two normal individuals and a patient with ataxia telangiectasia were used for comparison. The fibroblasts from the D-deletion retinoblastoma patient were significantly more sensitive to x-rays than those from the normal individuals, but not as sensitive as those from the ataxia patient. The two familial retinoblastoma strains displayed radiosensitivities intermediate between the D-deletion retinoblastoma strain and the normal strains. Skin fibroblasts from the patient with the D-deletion retinoblastoma are concluded to be abnormally radiosensitive. (10 refs.)

77-1091 **Giant Calcifying Epithelioma.** (Eng.) Sasaki, C. T. (Dept. Surgery, Section Otolaryngology, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT 06510) Yue, A.; Enriques, R. *Arch Otolaryngol* 102(12): 753-755; 1976.

A case is reported of a 21-yr-old man with a diagnosis of an enlarging pilomatrixoma. Initial biopsy of a right recurrent preauricular mass indicated a benign tumor. However, a subsequent deeper biopsy and extensive resection of the right auricle revealed a unique association of benign pilomatrixoma with aggressive infiltration of muscle and perichondrium by basaloid elements of the tumor. This composite mixed tumor is of particular interest because it demonstrates clinical transformation from a benign pilar tumor to one of a malignant nature. Transition in the direction of basal cell carcinoma supports the origin of basal cell epithelioma from hair follicles. This case illustrates the malignant potential of giant calcifying epitheliomas. (13 refs.)

77-1092 **Histochemical Characteristics of Mast Cells in Hemangiomas.** (Rus.) Shubich, M. G. (Dept. Histology, Kuban Medical Inst., Krasnodar, USSR) Lopunova, Z. K.; Zhulchenko, V. I. *Arkhl Patol* 38(12): 32-35; 1976.

The protein and carbohydrate contents of mast cells from hemangiomas were assessed histochemically in 40 patients with skin hemangiomas (21 capillary hemangiomas, 6 cavernous hemangiomas and 13 capillary hemangiomas with cavernous features) and in 17 patients with capillary hemangiomas of the mucous membrane of the mouth. The mast cells from all hemangiomas had elevated levels of cytoplasmic heparin. The increase in the heparin concentration was associated with an increase in the fibrinolytic activity due to the intensive synthesis of the heparin in the mast cells. (15 refs.)

77-1093 **Dermatome Areas and the Genesis of Melanomas.** (Eng.) Iyengar, B. (Dept. Pathology, Maulana Azad Medical Coll., New Delhi, India) *Indian J Cancer* 13(4): 330-332; 1976.

In a study of 65 malignant melanomas, a correlation was found between the length of the dermatome and the incidence of melanomas. Exact tumor locations were mapped out in relation to the distribution of dermatomes; the incidence of melanomas in relation to the length of the dermatome was calculated. The largest number of melanomas (23) were located in the feet, particularly along the distribution of L₅, which is the longest cutaneous nerve. Because there is a definite reciprocal relationship between the Schwann cells and the overlying dendritic melanocytes, and melanomas arise from a mixture of these two cells, the length of cutaneous innervation appears to influence melanoma genesis. Cells farther from the neural crest appear unstable and prone to malignant transformation by external carcinogenic agents. (11 refs.)

77-1094 **Quantitative Histochemical Analysis of Metabolic Enzymes in Human Melanomas and in Premalignant Lesions.** (Eng.) Cerimele, D. (Dept. Dermatology, Skin Aging and Cancer Res. Center, Univ. Pavia, Pavia, Italy) Torsellini, M. G.; Serri, F. *Pigm Cell* 2: 290-296; 1976.

Quantitative histochemical analysis of 14 enzymes of the main metabolic pathways (glycolysis, tricarboxylic acid cycle, pentose phosphate cycle, amino acid metabolism, and fatty acid metabolism) was performed on 10 human melanomas and on the lesions (nevi, 7 cases; lentigo maligna, 3 cases) from which they developed. In the premelanoma and in the melanoma, most of the enzymes studied, particularly those representative of the glycolytic pathway, showed a significantly increased activity in comparison with normal epidermis. The only exceptions were malic enzyme (NADP[±] malate dehydrogenase) and alanine transaminase, which were reduced by 50% in the melanoma. The finding that enzymes of the glycolytic pathway in human melanoma show a highly increased activity could be in agreement with, but it is not sufficient to affirm, the hypothesis that a cancer cell can originate because of impairment of respiratory metabolism, leading to markedly enhanced glycolysis. (12 refs.)

77-1095 **Chronicled Metastases in a Hamster Melanoma.** (Eng.) Paslin, D. (Dept. Dermatology, Sch. Medicine, Univ. California, San Francisco, CA 94143) Triglia, R. *J Invest Dermatol* 68(4): 194-195; 1977.

Fortner's melanotic melanoma #1 was injected into golden

hamsters to determine more specifically when metastases actually occur. Viable melanoma cells in suspension were injected into the right hindfoot of 86 hamsters. At 3, 7, 14, 21, and 28 days after inoculation, groups of hamsters underwent amputation of the right hindlimb at the right hip. Nine weeks after inoculation, all animals were sacrificed and the lungs were examined for metastases. No pulmonary metastases developed when amputations were done 3 or 7 days following inoculation. The data show that the incidence of pulmonary metastases increased as the time between inoculation and amputation increased. When amputation was performed on the 14th day, 17% of the hamsters developed metastases to the lung, but metastases occurred in 100% of the hamsters that did not undergo amputation until the 28th day. Pulmonary metastases were found to occur initially within 14 days of tumor inoculation. (3 refs.)

- 77-1096 Melanogenesis and Tumorigenicity in Melanoma Cells and Their Hybrids.** (Eng.) Hu, F. (Oregon Regional Primate Res. Center, Beaverton, OR) Pasztor, L. M.; White, R. L.; Wilson, B. J. *Pigm Cell* 2: 31-46; 1976.

B16 mouse melanoma cells (PAZG), which carry two distinct markers, pigmentation and tumor formation, were fused with mouse fibroblasts (LM(TK-)) and Chinese hamster cells (CH), which are neither pigmented nor tumorigenic, and the hybrids were analyzed for the expression or nonexpression of pigmentation and tumorigenicity. All of the hybrid cells were nonpigmented, but their tumorigenicity varied. With respect to pigmentation, the results support the view that when differentiated cells are fused with cells that do not express that differentiated function, the hybrids resemble the undifferentiated parent. The results indicate that tumorigenicity and lack of pigmentation in the hybrids are related to chromosome loss from the parental cells. Data from PAZG X CH hybrids suggest that tumorigenicity is a recessive trait. One hybrid line derived from PAZG X CH, however, was highly tumorigenic in spite of a drastic reduction in the number of melanoma chromosomes. (23 refs.)

- 77-1097 Factors Responsible for Platyfish-Swordtail Hybrid Melanoma--Many or Few?** (Eng.) Siciliano, M. J. (The Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX) Morizot, D. C.; Wright, D. A. *Pigm Cell* 2: 47-58; 1976.

Homogenates of different tissues from *Xiphophorus maculatus* (platyfish) and *X. helleri* (swordtails) and from their F₁, F₂, and backcross hybrids were subjected to vertical starch-gel electrophoresis followed by histochemical staining for over 30 proteins. The products of 64 genetic loci in the genus were resolved. Analysis of the polymorphisms at these loci

resulted in the recognition of 15 linkage groups within the system. The comparative frequency of all allozymes at 26 loci in platyfish (strain 163A) compared to various subspecies and species of swordtails to which 163A was hybridized, revealed no relationship between the genetic distance and severity of melanoma in the F₁ hybrids. In fact, the swordtail with the greatest genetic distance from 163A produced F₁ hybrids with the slowest growing and least severe melanomas. If the melanoma resulted from a general, nonspecific loss of genetic control in hybrids produced by highly divergent fish, the opposite result would be expected. The result obtained is consistent with the view that the melanoma is due to factors at a small number of loci. (19 refs.)

- 77-1098 Familial Melanoma.** (Eng.) Sutherland, C. M. (Dept. Surgery, Tulane Univ. Sch. Medicine, New Orleans, LA) *Pigm Cell* 2: 421-426; 1976.

Thirteen of 193 patients treated for malignant melanoma since 1972 had relatives with the same disease. Four other patients had relatives with either bone or soft tissue sarcomas. A pedigree of a kindred indicating the relationship of four siblings and a first cousin who have had nine primary malignant melanomas is presented. When routine records were maintained, an incidence of approx 1% of cases was found. When specific questions regarding relatives were asked of all 193 patients, the incidence rose to 6.7%. This suggests that many more patients have malignant melanoma in their families than has previously been recognized. (15 refs.)

- 77-1099 Chromosome I Heteromorphism in Patients with Malignant Disease; A Constitutional Marker for a High-Risk Group?** (Eng.) Atkin, N. b. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England) *Br Med J* 11(6057): 358; 1977.

Normal cells from 58 patients with malignant disease were assessed, either in blood cultures (47 cases) or in direct preparations or cultures of lymphoid or tumor tissue. Seventeen patients had received chemotherapy or radiotherapy. Peripheral blood samples from 12 normal individuals and from 36 patient with nonmalignant disease were used as controls. Cultured lymph nodes from 5 patients, spleen from 1 patient, and a fibroblast culture from a normal fetus were also evaluated, for a total of 55 controls. Chromosome preparations were stained by C banding. A total of 32/58 patients with malignant disease demonstrated heteromorphism, compared with 17/55 controls. This difference was statistically significant ($p < 0.01$). Nine of the 32 positive patients had received treatment. There is assumed to be a relation between the amounts of heterochromatin on the No. 1 chromosomes and susceptibility to at least some forms of malignant disease. (5 refs.)

77-1100 Nine Simultaneous Primary Tumors in a Boxer Dog. (Eng.) Priester, W. A. (Clinical Epidemiology Branch, NCI, NIH, Bethesda, MD 20014) Goodman, D. G.; Theilen, G. H. *J Am Vet Med Assoc* 170(8): 823-826; 1977.

Nine distinct primary tumors were found at necropsy in a 2-yr-old male boxer dog. These included a chemodectoma, osteosarcoma, bronchioloalveolar adenocarcinoma, interstitial cell tumor, seminoma, basal cell tumor, fibropapilloma, adrenal cortical adenoma, and pancreatic adenoma. Boxers, reported to be the most tumor-prone of all canine breeds, appear to be at high risk for chemoreceptor tumors, osteogenic sarcomas, testicular tumors, skin tumors, and endocrine gland tumors. It is suggested that a cytogenetic defect (immunologic or enzymatic) is responsible for this tendency toward tumor development. The significance of this information is related to the occurrence of familial cancers in humans. (19 refs.)

77-1101 Klinefelter's Syndrome and Extragenital Seminoma. (Eng.) Doll, D. C. (Dept. Medicine, West Virginia Univ. Medical Center, Morgantown, WV 26506) Weiss, R. B.; Evans, H. *J Urol* 116(6): 675-676; 1976.

A unique case of an extragenital metastatic seminoma in a 43-yr-old male with Klinefelter's syndrome is reported. Of particular interest is the presence of this germinal neoplasm in a syndrome associated with almost nonexistent germinal tissue. Because patients with Klinefelter's syndrome show an increased risk for certain cancers, the possible role of their XXY chromosomal complement in the development of malignancy is discussed. These findings indicate that this chromosomal aberration may make cells more susceptible to neoplastic transformation by SV-40 virus and possibly other oncogenic viruses. (6 refs.)

77-1102 Gonadal Malignancy and 46,XY Karyotype in a True Hermaphrodite. (Eng.) Szokol, M. (Pathological Inst., Univ. Medical Sch., 4012 Debrecen, Hungary) Kondral, G.; Papp, Z. *Obstet Gynecol* 49(3): 358-360; 1977.

A case of true hermaphroditism in a 24-yr-old patient, associated with gonadoblastoma and dysgerminoma is described. The gonadoblastoma had developed in a right gonad containing both immature ovarian and testicular tissue. The patient had a 46,XY karyotype; she considered herself a woman. The first diagnosis was strangulated inguinal hernia on the right side. (12 refs.)

77-1103 Condylomata Acuminata and Squamous Cell Carcinoma. (Eng.) Boxer, R. J. (Dept. Surgery, Div. Urology, Univ. California, Los Angeles, CA 90024) *Urology* 9(1): 72-78; 1977.

A 42-yr-old black man with simple condylomata acuminata developed squamous cell carcinoma in the same area 23 yr after the original diagnosis. This case is presented for the purpose of illustrating the transitory character of condylomata acuminata. (63 refs.)

77-1104 Pure Red Cell Aplasia. A Preleukemic State. (Eng.) Savage, R. A. (Dept. Lab. Hematology and Blood Banking, Cleveland Clinic, Cleveland, OH) *Cleve Clin Q* 43(4): 267-274; 1976.

A case of idiopathic pure red cell aplasia as a preleukemic manifestation of acute nonlymphocytic leukemia is presented. A 56-yr-old man was anemic following surgery for a renal calculus in December 1970. A diagnosis of pure-red-cell aplasia was made. Therapy with azathioprine, prednisone, 6-mercaptopurine, oxymetholone, and dexamethasone in various combinations failed to produce reticulocytosis. Most of his reticulocyte counts were <0.1%. He received 93 units of whole blood, packed cells, and WBC-poor packed cells within 23 mo. The patient then developed bronchitis. He was treated with ampicillin, but his symptoms persisted, and 1 mo later he was admitted with fever, splenic pain, and cough productive of yellow sputum. The spleen was now palpable 4 cm below the left subcostal margin, and a 5-cm hepatomegaly had appeared. A chest film revealed atelectasis of the middle lobe of the right lung. The patient died that afternoon after receiving the first dose of chemotherapy. Microscopic examination of the lungs demonstrated an infiltrate of malignant cells involving alveoli and parenchyma. The cells resembled histiocytes, with agranular pink to light blue cytoplasm, folded nuclei with chromatic clumping, and occasional, prominent nucleoli. Sections of spleen and lymph node showed extensive diffuse infiltration, with the malignant cells entirely obliterating the normal architecture. The spleen and several lymph nodes demonstrated leukemic thrombi with infarction similar to those found in the lung. The malignant cells entirely replaced the marrow. The liver displayed massive portal and periportal infiltration with malignant cells. Pure-red-cell aplasia seems to be another member of the ill-defined group of hematologic syndromes termed preleukemia. (22 refs.)

77-1105 Clinical Preleukemia in Infancy. (Ita.) Genova, R. (Universita degli Studi di Pavia, Istituto di Clinica Pediatrica, Pavia, Italy) Perinotto, G. *Minerva Med* 68(6): 397-404; 1977.

The preleukemic syndrome is characterized by hematologic alterations (anemia, thrombocytopenia, granulocytopenia) and bone marrow alterations (hypercellularity and erythropoietic, granulopoietic, and megakaryocytic alterations). The frequency of a preleukemic syndrome in infancy is much lower than at a later age and it does not have any special characteristics in infancy. The cases of two children, 3 and 8 yr old, with a clear preleukemic syndrome are presented. The clinical condition was marked pallor and anemia. In both cases, there was a severe alteration of the erythron and nuclear alterations of the erythroblasts. Sideremia was basically normal in one case and reduced in the other. Both patients required blood transfusions. One patient lived in apparent good health for about 4 yr, when an epilepticlike incident followed by the recurrence of anemia led to the diagnosis of acute undifferentiated leukemia. The clinical and hematologic signs of the other patient, however, never really improved. (8 refs.)

- 77-1106 **Syndrome of Shwachman and Leukaemia.** (Eng.) Huijgens, P. C. (Dept. Internal Medicine, Free Univ. Hosp., De Boelelaan 1117, Amsterdam, Netherlands) Van Der Veen, E. A.; Meijer, S.; Muntinghe, O. G. *Scand J Haematol* 18(1): 20-24; 1977.

The case of a 23-yr-old man with Shwachman's syndrome who died of acute myeloblastic leukemia after a period of neutropenia and sideroblastic anemia is reported. Immature granulocytopoiesis, acquired Pelger-Huet anomaly, and sideroblastic anemia were a suggestive combination of symptoms, of preleukemia. A later diagnosis of acute myeloblastic leukemia was made. It is concluded that the hematological abnormalities in Shwachman's syndrome patients, such as the case described, might indeed be signs of preleukemia. (14 refs.)

- 77-1107 **SV40 T-Antigen Expression in Skin Fibroblasts from Clinically Normal Individuals and from Ten Cases of Fanconi Anemia.** (Eng.) Lubiniecki, A. S. (Life Sciences Div., Meloy Labs., Incorporated, Springfield, VA 22151) Blattner, W. A.; Dosik, H.; Sun, C.; Fraumeni, J. F. *Am J Hematol* 2(1): 33-40; 1977.

Skin fibroblast cultures from 76 healthy subjects (38 men, 38 women; 44 white, 32 black) were examined in an effort to define the normal range of T-antigen expression. The fibroblasts were tested for expression of simian virus 40 (SV40) T antigen by indirect immunofluorescence. The data were normally distributed, with no differences among the age, sex, or ethnic groups tested (Afro-American, Haitian, Anglo-Saxon, Puerto Rican, Jewish, Indian, Hungarian, and Italian). The role of infrequent karyological anomalies on T-antigen

expression within the normal population was also determined. The expression of SV40 T-antigen did not differ significantly between individuals whose metaphase chromosomes exhibited detectable hyperdiploidy, tetraploid breaks, endoreduplications, fragments, exchanges, or translocations and individuals whose karyotypes were free of such defects. Karyological analysis of both peripheral WBC and or skin fibroblasts detected excessive chromosomal instability in all 10 cases of Fanconi anemia (7 men, 3 women aged 1-3 yr). Fibroblasts from Fanconi anemia patients expressed SV40 T-antigen 4.5 times more often than cells from healthy individuals. Nine of the 10 cases exceeded the 5% confidence limit. No clear correlation existed between T antigen value and clinical findings or the type or degree of cytogenetic abnormality in the skin fibroblast cultures. Elevated T-antigen expression in Fanconi anemia fibroblasts reflects a defect at the cellular level. (15 refs.)

- 77-1108 **Familial Cancer on a Scottish Island.** (Eng.) Hill, R. D. (No affiliation given) *Nurs Mirror* 144(8): 54-55; 1977.

The occurrence of three unusual cases, two of acute lymphoblastic leukemia and one of Fanconi's anemia, in a small medical practice in Scotland led to investigation of the families of the children with these diseases. It was found that the three children were related; that two other children in the family had Marfan's syndrome, and that of 18 deaths in the family that were investigated, 10 were caused by a neoplasm (no refs.)

- 77-1109 **Comparable Complex Rearrangements Involving 8;21 and 9;22 Translocations in Leukaemia.** (Eng.) Lindgren, V. (Dept. Medicine and Franklin McLean Memorial Res. Inst., Univ. Chicago, Chicago, IL 60637) Rowley, J. D. *Nature* 226: 744-745; 1977.

Chromosomal rearrangements observed by banding techniques in patients with acute myelocytic leukemia (AML) and chronic myelocytic leukemia (CML) are discussed. In each case, two chromosomes were preferentially involved in translocation. In AML, a translocation between approximately one-third of the long arm of chromosome 8 to the end of chromosome 21 commonly occurs. Additionally, fluorescent analysis of the cells of a female patient revealed a translocation between chromosome 8 and the long arm of chromosome 17 with a concomitant loss of an X chromosome in 22/26 cells prior to therapy and in 5/10 cells after chemotherapy. Reexamination of this patient showed an analogous aberration of chromosome 21 compatible with a translocation from 17q (corrected karyotype 45,X,t(8;17;21)(q22;q23;q22)). The cells of a second female patient revealed a translocation from

chromosome 8 to the short arm of chromosome 11 with addition of one 8 chromosome. One chromosome 21 appeared larger than normal due to the presence of a narrow band of fluorescent material; (karyotype: 47 XX, +8,t(8;11;-21)(q22;p15;q22)). In 413/440 CML patients a portion of the long arm of chromosome no 22 was translocated to the end of the long arm of chromosome no 9. These findings indicate that chromosomal alterations are among the fundamental changes resulting in malignancy. (6 refs.)

77-1110 Cold Agglutinins in a Case of Chronic Lymphatic Leukaemia. A Study of the Lymphocyte Surface. (Eng.) Greally, J. F. (Dept. Immunology, Sch. Pathology, Trinity Coll., Dublin 2, Ireland) Whelan, C. A.; O'Connell, L.; O'Gorman, D. *Acta Haematol* 57(4): 206-210; 1977.

Studies were conducted on the peripheral blood lymphocytes from a 64-yr-old man with chronic lymphocytic leukemia (CLL). Initial observations that large numbers of these lymphocytes formed rosettes with unsensitized sheep RBC and displayed 100% fluorescence using anti-human immunoglobulin M (IgM) prompted these further studies. A cold agglutinin IgM was found in the patient's serum and on the cell surface, as determined by immunofluorescence using anti-human IgM. Rosetting tests indicated the presence of lymphocytes of varying maturity with B- and T-cell markers. The patient was treated with chlorambucil, and the lymphocyte count and other hematological parameters returned to near normal levels, although the monoclonal nature of the circulating lymphocytes persisted. More than 70% of the lymphocytes still bore K-type IgM on their surface. (8 refs.)

77-1111 Chronic Myelomonocytic Leukemia. An Ultrastructural Study by Transmission and Scanning Electron Microscopy. (Eng.) Skinnider, L. F. (Dept. Pathology, Univ. Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W8) Card, R. T.; Padmanabh, S. *Am J Clin Pathol* 67(4): 339-346; 1977.

The hematologic findings in three cases of chronic myelomonocytic leukemia (CML) are presented along with the results of ultrastructural studies in two of the cases. The patients were all elderly, two being > 80 yr old. There was a marked leukocytosis in the peripheral blood plus two distinct nonlymphocytic populations, one of granulocytes and one of monocytes. In the marrow the granulocytic element was strikingly hyperplastic and there was a marked increase in blast cells. Earlier forms such as promyelocytes and myelocytes were also increased. Electron microscopy showed marked nuclear abnormality in the granulocytes and nuclear cytoplasmic organelle asynchrony. In the marrow, atypical forms and intermediate cells difficult to distinguish from

monocyte precursors were evident. The ultrastructural findings support the view that most leukemic cells in the marrow are granulocytic, although there were many cells that were difficult to allocate to either cell line. These indeterminate cells may indicate that the leukemic cell has the potentiality of monocytic as well as granulocytic differentiation and that CML is part of the same disorder as acute myelomonocytic leukemia. (16 refs.)

77-1112 The Peripheral Blood in Chronic Granulocytic Leukaemia. Study of 50 Untreated Philadelphia-Positive Cases. (Eng.) Spiers, A. S. (Div. Medical Oncology, Boston Univ. Medical Center, 75 East Newton St., Boston, MA 02118) Bain, B. J.; Turner, J. E. *Scand J Haematol* 18(1): 25-38; 1977.

The hematological findings in the peripheral blood of 50 patients (27 women, 23 men) in whom chronic granulocytic leukemia (CGL) had been diagnosed and who were subsequently demonstrated to be Philadelphia chromosome-positive were evaluated. Each of three observers performed a differential WBC count on 500 cells in each blood film. There was no significant difference in Hb concentration between the sexes. There was a loose inverse correlation between Hb concentration and total WBC count: Hb values < 8 g/deciliter (dl) were observed at all levels of WBC count, but Hb concentrations > 12 g/dl did not occur with WBC counts > 250 x 10⁹/liter. The variation of Hb with WBC count was independent of sex. The platelet counts had no fixed relation to the total WBC count. Six patients (12%) had platelet counts < 220 x 10⁹/liter. In all six, the WBC count was < 250 x 10⁹/liter. There was no significant sex difference in total WBC count. Only 26% of counts were < 100 x 10⁹/liter, and 24% were > 300 x 10⁹/liter. With the exception of the metamyelocytes, there was a direct correlation between the degree of maturity of the granulocytic cells and their percentage in the differential WBC count. As the total WBC count rose, the percent of neutrophils fell (while that of immature granulocytic forms rose), the myelocytes and neutrophils became more obvious, the percent of lymphocytes and monocytes decreased, and the percent of basophils and eosinophils declined. Although the percent of both blasts and myelocytes increased with total WBC count, the proportion of blasts increased more slowly. All patients had absolute basophilia, 46 had absolute eosinophilia, and 39 had absolute monocytosis. In 27 patients, the total lymphocyte count was above normal. Nucleated RBC were observed in the peripheral blood in 49 patients. Mitotic figures were seen in seven patients: the av WBC count in these patients was 329 x 10⁹/liter, or 46% higher than the av count for all 50 patients. Of the great variety of anomalies observed, only nucleated RBC, unclassified WBC, and eosinophil myelocytes were common. Application of the findings should improve the accuracy of the hematological diagnosis of CGL. (20 refs.)

- 77-1113 Appearance of Ph¹ Chromosome During the Course of Polycythemia Vera Transformed to Subacute Myeloid Leukemia.** (Fre.) Bousser, J. (Service d'Hematologie, Hotel-Dieu, 1, pl. du Parvis Notre-Dame, F 75004 Paris, France) Zittoun, R.; Casin, I.; Turleau, C.; De Grouchy, J. *Nouv Presse Med* 6(9): 753-754; 1977.

The patient developed polycythemia vera at the age of 58, and the disease progressed to myeloid leukemia over a period of 9 yr. The patient was treated with frequent bleeding and ³²P. A karyotype, performed about a year before the appearance of myeloblasts and promyelocytes, revealed a chromosome aberration but not the Philadelphia (Ph¹) chromosome. Leukocytosis increased progressively, as did splenomegaly. The Ph¹ chromosome was observed in the ninth year of disease, concurrently with a bone marrow profile of 10% myeloblasts and 16% promyelocytes. Also, a chromosome in group B (chromosomes 4 and 5) in all the cells of the karyotype was replaced by an element having a centralized centromere (M marker). A brief remission occurred after hydroxycarbamide treatment, but the patient died of bone marrow aplasia in the 10th year of the disease. Two additional karyotypes showed the Ph¹ chromosome in every cell plus additional chromosome aberrations. (11 refs.)

- 77-1114 Altered Platelet Surface Glycoproteins in Chronic Myeloid Leukemia.** (Fre.) Vainer, H. (Institut de Recherches sur les Maladies du Sang et sur les Leucemies, Hopital Saint-Louis, 75475 Paris, France) Bussel, A. *Int J Cancer* 19(2): 143-149; 1977.

The polypeptide and glycoprotein (GP) electrophoretic patterns of platelets and platelet membranes, solubilized under dissociating conditions, were studied for four patients with chronic myeloid leukemia (CML). No differences in polypeptide patterns were detected in the platelets from normal and CML subjects. As is usual with CML, the total number of platelets was normal (3/4) or slightly augmented (1/4). The GP modification of the electrophoretic banding visualized by the PAS reagent consisted for the CML patients in the decrease of the 155,000-dalton GP I; the presence of two PAS-positive bands in the area of the 135,000-dalton, normal, PAS-positive GP III; and a variable decrease of the 100,000-dalton GP III. Preliminary data showed an increased catalytic transfer of the labeled galactosyl and N-acetylgalactosaminyl residues from the exogenous nucleotide ¹⁴C sugar precursors on to the CML-platelet endogenous sugar acceptors. The altered GP metabolism in CML platelets may explain the impaired platelet adhesion and aggregation occurring in CML patients. (36 refs.)

- 77-1115 Light Green Crystals in May-Grunwald and Giemsa-Stained Bone Marrow Macrophages in Patients with Myeloid Leukaemia.** (Eng.) Stavem, P. (Sec-

tion Haematology, Medical Dept. A, Rikshospitalet, Oslo, Norway) Ly, B.; Bjornekleit, A. *Scand J Haematol* 18(1): 67-72; 1977.

Since an unusually large number of macrophages containing crystalline inclusions that stained light green with May-Grunwald and Giemsa stains, were observed in the bone marrow of a patient in the terminal stage of acute myelomonocytic leukemia (AML) further cytochemical and ultrastructural studies were made for similar inclusions in other leukemia patients. The inclusions were not observed in any of the four patients with chronic lymphocytic leukemia or in the six with acute lymphoblastic leukemia. However, inclusions were noted in 3/5 cases of chronic myeloid leukemia and in 2/5 cases of AML. (5 refs.)

- 77-1116 Primary and Secondary Granule Contents and Bactericidal Capability of Neutrophils in Acute Leukaemia.** (Eng.) Odeberg, H. (Dept. Internal Medicine, Univ. Lund, Lund, Sweden) Olofsson, T.; Olsson, I. *Blood Cells* 2(3): 543-551; 1976.

Abnormalities of cytoplasmic maturation and function of neutrophils isolated from 20 patients with acute granulocytic leukemia and 3 with acute myelomonocytic leukemia in relapse are described. Primary granule constituents were determined by immunochemical methods. Bactericidal activity against *Escherichia coli* and *Staphylococcus aureus* as well as phagocytic rate and oxygen consumption during phagocytosis was determined in some cases. Lactoferrin was not detectable in 8/23 patients and was decreased in most. In 7/23 patients with low myeloperoxidase content, other granule constituents measured were also low. Elastase deficiency was found in one patient. Bactericidal activity against *E. coli* was defective in 4/17 patients. In eight patients tested, four showed defective killing of *S. aureus* but three of those killed *E. coli* normally. Rate of ingestion of opsonized paraffin oil droplets was normal in 7/8 patients. Oxygen consumption during phagocytosis showed normal or supernormal increments in 8/11 patients. Reduced oxygen consumption correlated with deficient killing of *E. coli* or *S. aureus*. There was no correlation between neutrophil content and bactericidal activity. It is suggested that the abnormalities noted are due to a leukemic origin of the mature-appearing neutrophils. (26 refs.)

- 77-1117 Kinetic Analysis of the Aggressiveness of Acute Leukemia.** (Rus.) Vladimirskaia, E. B. (Clinical Hematological Lab., Inst. Pediatrics, USSR Acad. Medical Sciences, Moscow, USSR) Averbakh, A. V. *Probl Gematol Pereliv Krovi* 22(1): 3-7; 1977.

Characteristics of the proliferation of leukemic blast cells were studied in 41 adults and in 17 children with acute leukemia. There were 10 children with acute lymphoblastoid leukemia (5 were in acute phase and 5 in relapse) and 7 children with acute myeloid leukemia (4 in acute phase and 3 in relapse); among adults, 20 had acute lymphoblastoid leukemia (10 in acute phase and 10 in relapse) and 21 had acute myeloid leukemia (16 in acute phase and 5 in relapse). The H-thymidine labeling index was determined and the results were reported as the percent of dividing cells (p). In adults the av p value was significantly higher for the patients in relapse ($66.0 \pm 18.2\%$) than for the patients in acute phase ($50.0 \pm 10.0\%$). Of 13 patients who in the initial phase of the disease had $p > 60\%$, only 2 entered into even a short remission. Of 13 patients with $p < 60\%$, 6 entered into complete clinical remission. Results were similar for children. There was no statistically significant difference between the mean values of p in the patients with acute lymphoid and acute myeloid leukemia. (5 refs.)

77-1118 **Esterase Activity in Erythroleukemia.** (Eng.) Kass, L. (Dept. Internal Medicine, Simpson Memorial Inst., Univ. Michigan, Ann Arbor, MI 48109) *Am J Clin Pathol* 67(4): 368-370; 1977.

Bone marrow from 10 normal individuals and 6 patients with untreated erythroleukemia was examined for esterase activity. All of the patients died shortly after diagnosis; acute myelomonocytic leukemia developed in one patient 4 days after the diagnosis of erythroleukemia was made. Neither specific nor nonspecific esterase activity was detected in the erythroid precursors obtained from the bone marrow of the 10 normal individuals, but both were detected in the abnormal erythroid precursors from the 6 patients. The findings suggest that the abnormal erythroblasts in erythroleukemia possess properties of granulocytes. However, it is not possible to state that the neoplastic erythroid precursors containing properties of granulocytes are actually capable of transforming into myeloblasts or neoplastic granulocytes. The findings are more consistent with the viewpoint that there may be a stem cell or clone of stem cells, probably myeloblastic, common to granulocytic and erythroid precursors alike. The results also provide support for the theory that erythroleukemia is part of the framework of the DiGuglielmo syndrome, in which the eventual outcome is often acute myeloblastic or myelomonocytic leukemia. (22 refs.)

77-1119 **Acute Erythroleukemia Complicating Prolonged Chemotherapy for Ovarian Carcinoma.** (Eng.) Khandekar, J. D. (Section Medical Oncology, Evanston Hosp., Evanston, IL) Kurtides, E. S.; Stalzer, R. C. *Arch Intern Med* 137(3): 355-356; 1977.

The effect of duration of chemotherapy relative to carcinogenicity was examined. The clinical series included two patients with protracted chemotherapeutic management of ovarian carcinoma who subsequently developed leukemia. A 39-yr-old woman received chlorambucil (10-12 mg/day, po) for 18 mo after total abdominal hysterectomy and bilateral adnexectomy for ovarian carcinoma. Omental carcinoma was preoperatively confirmed. Chlorambucil was resumed after a 6-mo interruption for pancytopenia; treatment continued another 12 mo before intractable pancytopenia forced a second suspension. The patient received a total of 10,000 mg of drug in 36 mo. Although earlier marrow biopsies had been consistent with hypoplasia, subsequent biopsies confirmed erythroleukemia. A 68-yr-old woman received chlorambucil (6 mg/day, po) for 4 yr, for a total of 6,000 mg, along with 4,000 rads of telecobalt irradiation to the pelvis following total hysterectomy for abdominal extensions of right ovarian adenocarcinoma. The marrow was markedly hypercellular, with a pronounced left shift and bizarrely nucleated RBC. Several months later, a marrow aspirate showed erythroleukemic signs. It is not clear whether the therapy or the known capacity of cancer patients to increased frequency of second malignancies is responsible for the leukemogenesis. Most of the nine other cases of acute leukemia following alkylating chemotherapy were cured of the first tumor before the onset of the iatrogenic leukemia. (11 refs.)

77-1120 **"Hairy Cell" Leukemia -- A Special Form of B Cell Lymphocytic Leukemia.** (Rus.) Iavorkovskii, L. I. (Dept. Leukemia Res., Riga Medical Inst., Riga, USSR) Press, B. O.; Solovei, D. I. *Probl Gematol Pereliv Krovi* 22(1): 46-50; 1977.

The morphological and clinical features of leukemic reticulo-endotheliosis (hairy-cell leukemia) are reviewed and two cases are presented. The first patient was admitted to the hospital with easy bruising and splenomegaly. More than 80% of lymphoid cells had typical irregular surface outlines and numerous extensions from the cell membrane. She was treated with prednisone and vitamins and at the time of report (3.5 yr later) was in satisfactory condition. The 2nd patient (a 44-yr-old man) had leukopenia (3,600) and marked splenomegaly. In the peripheral blood two types of lymphoid cells were observed: about 75% had regular cell surfaces and 25% had fuzzy outlines and numerous extensions from the cell membranes. He underwent splenectomy and was discharged in good health. (15 refs.)

77-1121 **Endogenous Peroxidase Activity in Leukemia Cells in Hairy Cell Leukemia.** (Fre.) Reyes, F. (Unite de Recherches sur les Anemies, I.N.S.E.R.M. U. 91, Hopital Henri-Mondor, 94010 Creteil, France) Gourdin, M.

F.; Farcet, J. P.; Dreyfus, B.; Breton-Gorius, J. *C R Acad Sc [D]* (Paris) 284(6): 493-496; 1977.

Mononuclear blood cells were studied ultrastructurally and by immunocytochemistry in three cases of hairy cell leukemia. The origin of the characteristic mononuclear cell, present also in bone marrow and spleen, remains obscure, although evidence supports a B-lymphocyte relationship. Immunoglobulin G (IgG) was heavily concentrated on the membrane villi of all the monocytes; IgM, IgD, and the light-chain kappa and lambda Ig were less uniformly distributed. Endogenous peroxidase was observed in the perinuclear space and endoplasmic reticulum of cells fixed in a mixture of aldehydes diluted in tannic acid and, also, in cells incubated in a mixture of diaminobenzidine and Ringer's solution. The peroxidase activity indicates a nonlymphocytic origin of the mononuclear cell and a relationship to the mononuclear phagocyte system. (20 refs.)

77-1122 Motility of Acute Human Leukemia Cells: A Study by Time-Lapse Cinematography and Scanning Electron Microscopy. (Eng.) Haemmerli, G. (Div. Cancer Res., Inst. Pathology, Univ. Zurich, Birchstrasse 95, CH-8050 Zurich, Switzerland) Felix, H. *Blood Cells* 2(3): 415-430; 1976.

Time-lapse cinematography and scanning electron microscopy (SEM) of cells from three lymphoid and three myeloid leukemia cases revealed a close correlation between the dynamic state of the cells and their surface morphology. There was a close correlation between the various shapes assumed by leukemia cells during their on-spot and locomotive activities and their SEM appearance. SEM also revealed details of surface architecture, such as cytoplasmic extension and attachment devices, not visualized by either phase contrast or interference contrast microscopy. As has been indicated by prior studies, the interpretation of the static morphology as indicated by SEM in terms of dynamic behavior, as recorded by time lapse photography, is only permissible if the two methods are used concurrently and under identical conditions during the preparatory phase. (8 refs.)

77-1123 Variations in the Levels of Certain Amino Acids in the Course of Leukemia. (Fre.) Loeper, J. (Laboratoire de Medecine Experimentale, C.H.U. St-Antoine, 27, rue de Chaligny, F 75571 Paris Cedex 12, France) Debray, J.; Cottet, J.; Loeper, J. *Nouv Presse Med* 6(7): 539-543; 1977.

The hyperuricemia frequently observed in leukemic patients results from catabolism of the nucleoproteins of excessive numbers of leukemic cells and from faulty renal excretion of

uric acid. In order to determine the source of the uric acid blood levels of the amino acids, measured by column chromatography, were compared for 17 patients with acute myeloid leukemia (AML); 22 patients with chronic myeloid leukemia (CML); and 25 controls. Amino acids were also measured in three patients with lymphoid leukemia, two with Hodgkin's disease, three with refractory anemias, and six with polycythemia; however, levels in these patients were similar to controls. The av levels of the amino acids for the AML and CML patients and the controls are tabulated in terms of percentage values or absolute values (micromoles/100 ml serum). The percentages of glycine and cystine increased for the AML and CML patients; α -alanine increased and threonine and histidine decreased in the AML patients. In contrast to literature reports, only a nonsignificant increase in tryptophan was observed in these leukemic patients. There was a significant positive correlation between the percentage of myeloblasts in the blood and glycine and tryptophan levels. The av total quantity of amino acids was more constant in the controls; there was a nonsignificant augmentation of av levels with a wider dispersion of values in the leukemic group. (9 refs.)

77-1124 Surface Features of Cells in Human Lymphoproliferative Disorders. An Immunoelectron Microscopy Study. (Eng.) Gourdin, M. F. (Unite de Recherches sur les Anemies. INSERM. U. 91 Hopital Henri Mondor, 94010 Cretell, France) Reyes, F.; Lejone, J. L.; Mannoni, P.; Dreyfus, B. *Haematol Bluttransfus* 19: 207-219; 1976.

The feasibility of classifying various lymphoproliferative disorders on the basis of cellular surface features as detected by immunoelectron microscopy was investigated. Peroxidase conjugated antibodies were applied to cell suspensions after glutaraldehyde fixation in order to detect surface associated immunoglobulins (IgS). Whatever the class of IgS, labeled B-lymphocytes from eight normal individuals had a characteristic appearance due to numerous microvilli. Samples from 10 patients with untreated chronic lymphocytic leukemia (CLL) confirmed the relationship between the presence of IgS and a villous surface, as previously reported. In some samples, the surface morphology ranged from moderately villous to hairy cells. Some cells exhibited a polar concentration of labeled microvilli with a remaining smooth surface; some cells had a rather smooth surface and few microvilli. Smooth labeled B-lymphocytes were still more obvious in blood samples from four patients with prolymphocytic leukemia. Specimens contained variable proportions of small villous B-lymphocytes and a minor population of blastic smooth B cells. In two cases of Waldenstrom macroglobulinemia, a villous surface characterized the mature lymphocytes, as in CLL. In blood specimens from two patients with Sezary syndrome, the lymphocytes were regularly free of labeling by anti-immunoglobulin reagents, although segments of their membrane exhibited numerous microvilli, with the remaining surface being smooth. The abnormal mononuclear cells from

four cases of hairy cell leukemia exhibited the following main characteristics: a very irregular surface covered by numerous long microvilli and finger-like projections; a high density of associated IgS; a lack of detectable endogenous peroxidase in either the endoplasmic reticulum or granules. Overall these observations of B and T cell disorders emphasize that surface morphology alone is not a suitable criterion for classifying cells of lymphoproliferative disorders. (28 refs.)

77-1125 Surface Membrane Changes in Lymphocytes from Patients with Infectious Mononucleosis.

(Eng.) Mintz, U. (Dept. Genetics, Weizmann Inst. Science, Rehovoth, Israel) Sachs, L. *Int J Cancer* 19(3): 345-350; 1977.

Peripheral blood lymphocytes from 20 patients with acute infectious mononucleosis (IM) were evaluated for cell aggregation and for cap formation by concanavalin A (Con A). Cap formation by Con A in the isolated peripheral blood mononuclear cells was much lower in the IM patients than in 20 normal persons. The lymphocytes from the patients differed from the normal lymphocytes by demonstrating a high degree of cell aggregation, even in the absence of Con A. Four patients with acute IM were tested after clinical remission, when there were no clinical symptoms of IM and no atypical lymphocytes. The results indicated that the frequency of cap formation had changed from 5.4% at the time of acute IM to 14.5% 3 mo later. The lymphocytes from the IM patients were enriched for B and T cells by further gradient centrifugation. The high degree of cell aggregation without Con A occurred only with B cells, but there was a low frequency of cap formation in both B and T cells. A high degree of B-cell aggregation and a low percentage of T and B cells with a Con A-induced cap are associated with acute IM. (22 refs.)

77-1126 Coeliac Disease with Hodgkin's Lymphoma.

(Eng.) Seggie, J. (Watford General Hosp., Watford, Hertfordshire, WD1 7HH, England) *Proc R Soc Med* 69: 946-947; 1976.

A 30-yr-old woman with coeliac disease continued to respond to a gluten-free diet but at the same time developed progressive Hodgkin's disease despite early treatment. The dissociation in clinical progress may be due to the extra-abdominal distribution of the Hodgkin's lymphoma. (6 refs.)

77-1127 Mediterranean Lymphoma (Diffuse Immunoblastic Small Intestinal Lymphoma) without

IgA Abnormality. (Fre.) Galian, A. (Service Central d'Anatomie et Cytologie Pathologiques, Hopital Saint-Lazare, 107, rue du Faubourg-Saint-Denis, F 75475 Paris Cedex 10, France) Scotto, J.; Rouffy, J.; James, J. M.; Lenormand, Y.; Rambaud, J. C. *Gastroenterol Clin Biol* 1(1): 49-58; 1977.

A 22-yr-old Algerian man had a diffuse lymphoma of the small intestine characteristic of Mediterranean lymphoma, but without immunofluorescent evidence of intracytoplasmic abnormal immunoglobulin A (IgA). The patient was admitted to the hospital in 1972 for chronic abdominal pain and diarrhea, intermittent since 1966, and cachexia. A barium x-ray study of the gastrointestinal tract in 1970 showed a normal stomach, but hypertrophy of the mucosal folds of the proximal jejunum as well as fragmentation and concentration of barium in the adjacent small intestine. No abdominal masses or hepatosplenomegaly was noted at that time. The patient had tetanus and neurological symptoms related to a hypoparathyroidism that were rapidly cured by 10 mg of dihydrotachysterol and 1 mg calcium/day for 8 days. Clinical examination on present admission revealed edema of the lower limbs, pleural and pericardiac effusions, and a hard abdominal mass in the umbilical area. Liver and spleen were not enlarged. Biopsy of an enlarged axillary lymph node showed a malignant lymphoma. Immunofluorescent studies of the axillary and mesenteric nodes and the small intestine demonstrated normal IgA and IgM in the plasmocytes that had infiltrated the wall of the entire small intestine and the nodes, but no fluorescence. Electrophoresis of the serum showed a hyper α 2-globulinemia (10.5 and 15 g/liter), but no other abnormal globulin fractions. Bence-Jones proteins and abnormal α -chain IgA were absent from the urine. The patient died of hemorrhage 2 mo after admission. Differences between this case and the usual cases of Mediterranean lymphoma are discussed. (21 refs.)

77-1128 Establishment in Continuous Culture of a New Type of Lymphocyte from a "Burkitt-like"

Malignant Lymphoma (Line D.G.-75). (Eng.) Ben-Bassat, H. (Chanock Centre for Virology, Hebrew Univ. Hadassah Medical Sch. Jerusalem, Israel) Goldblum, N.; Mitrani, S.; Goldblum, T.; Yoffey, J. M.; Cohen, M. M.; Bentwich, Z.; Ramot, B.; Klein, E.; Klein, G. *Int J Cancer* 19(1): 27-33; 1977.

The isolation and characterization of a previously unknown type of lymphocyte from pleural effusions of a patient with primary abdominal lymphoma are reported. A 10-yr-old boy presented with a large colonic mass and enlarged mesenteric nodes, following abdominal pain of 2 wk duration. Biopsy showed a Burkitt's type lymphoma in both tumor and nodes. Cyclophosphamide (40 mg/kg/day) led to clinical remission, but maintenance by cyclophosphamide and radiotherapy to the primary tumor could not forestall a recurrence with pleural effusion beyond 3 mo. The cells harvested and cultivated from the pleural effusion (line D.G.-75) possessed several

properties differentiating them from known lymphoblastoid lines. There was rapid proliferation after an 8-wk lag phase, with a doubling time of 18-20 hr. The cells appeared to be normal, without the typical "hand-mirror"-shaped lymphoblastoid configuration. The modal chromosome number was 46, and there was an apparent asymmetry in the homology of chromosome 14. The D.G.-75 cells were negative for Epstein-Barr virus nuclear antigen and surface receptors. They were only weakly agglutinable by concanavalin A, but cap formation was prominent. Surface immunoglobulin M (IgM) was detected, which suggests a B-cell origin for the line. The anti-IgM sera stained more strongly than the anti-kappa sera, but only IgM-kappa chains were detected in the early passages. Histologically, the cells bore a marked resemblance to lymphocyte precursors in bone marrow. There could be two different types of Burkitt's lymphoma, and D.G.-75 could represent the type lacking Epstein-Barr virus. (40 refs.)

- 77-1129 Electron Microscopic Investigation of Cell Elements and Interstitial Substance of Osteogenic Sarcoma.** (Rus.) Litvinova, L. V. (Lab. Pathological Anatomy Skeletal Tumors, Dept. Pathological Anatomy Human Tumors, Scientific Center Oncology, USSR Acad. Sciences, Moscow, USSR) *Arkiv Patol* 38(12): 36-40; 1976.

The ultrastructure of the osteogenic sarcoma tissue was studied. Four different cell types were observed. Chondroblastic, osteoblastic, fibroblastic and undifferentiated cells in the tumor tissue were found to retain typical features of the normal osteogenous tissue. Distribution of alkaline phosphatase in the tumoral chondroblasts was similar to that in the normal chondroblasts. The presence of cross-striated collagen fibers in the chondroid zones of the tumor, and their absence in the osteoid zones, indicates a decreased synthesis of mucopolysaccharides in the interstitial tissue of the osteogenic sarcoma. (10 refs.)

- 77-1130 Intramuscular Iron and Local Oncogenesis.** (Eng.) Robertson, A. G. (Centre for Rheumatic Diseases and Univ. Dept. Medicine, Royal Infirmary, Glasgow G4 OSF, Scotland) Dick, W. C. *Br Med J* 1(6066): 946; 1977.

A 35-yr-old woman presented with a 4-mo history of pain and swelling in the left hip. Examination showed a large craggy mass in the left gluteal region, and biopsy revealed a poorly differentiated spindle cell fibrosarcoma. Strainable iron could not be detected. Radiotherapy was administered to the tumor site. On further questioning, it was learned that the patient had received a short course of iron dextran after the delivery of one of her children 14 yr earlier. One injection was given into the right gluteal muscles, after which the patient developed a mass in that area. Four injections were given into

the left gluteal muscles. There was no history of other allergies or of other im injections into the buttocks. Animal studies have shown that sarcomas readily occur at the site of large im injections of iron. The incidence in man is much rarer, possibly due to the larger sizes of the muscles. A long induction period may also be needed in man. (7 refs.)

- 77-1131 Sclerosing Reticulum Cell Sarcoma following Prolonged Treatment with Azathioprine for Idiopathic Thrombocytopenic Purpura.** (Eng.) Nord, E. (Tel-Aviv Univ. Medical Sch., Dept. Internal Medicine 'D', Beilinson Medical Center, Petah Tikva, Israel) Douer, D.; Kessler, E.; Pinkhas, J.; De Vries, A. *Scand J Haematol* 17(5): 321-325; 1976.

A case of sclerosing reticulum cell sarcoma following prolonged treatment with azathioprine for idiopathic thrombocytopenic purpura in a 56-yr-old woman is presented. The patient was admitted in 1975 for investigation of axillary lymphadenopathy. Since the age of 16, she had recurrent hemorrhages and menorrhagia. Thrombocytopenia (platelets 30×10^9 /liter) was first documented at the age of 26. Physical examination at that time revealed numerous ecchymoses, a palpable spleen and absence of lymphadenopathy. At the age of 36, the patient had a platelet count of 2×10^9 /liter; thromboagglutinins were not found. Following a 3 mo course of ACTH, the ecchymoses disappeared, but the platelet count remained unchanged. In 1957, prednisone (60 mg daily) was begun, and the platelet count reached a max of 70×10^9 /liter; prednisone treatment (40 mg daily) was continued for 4 yr. Physical examination in 1961 revealed a moon face, a buffalo hump, and numerous petechiae and ecchymoses. The spleen was palpable 4 cm below the costal margin, and the platelet count was 6×10^9 /liter. An aspiration bone marrow biopsy smear demonstrated numerous megakaryocytes. A duodenal ulcer was shown roentgenologically, and steroid therapy was discontinued. The patient was seen again in 1966 with diffuse ecchymoses, splenomegaly, but no lymphadenopathy. The platelet count was 10×10^9 /liter, and splenectomy was performed. The platelet count rose temporarily to 85×10^9 /liter, but since the bleeding tendency recurred, prednisone (10 mg daily) was readministered. In 1968, while the platelet count was 10×10^9 /liter, prednisone therapy was discontinued because of reactivation of the duodenal ulcer, and azathioprine (100 mg daily) was begun. Within 8 wk, the platelet count rose to 170×10^9 /liter, and there was a significant improvement in the bleeding tendency. In March 1975, axillary lymphadenopathy was observed. An axillary lymph node biopsy revealed sclerosing reticulum cell sarcoma. Cyclic chemotherapy, consisting of iv cyclophosphamide (10 mg/kg) and vincristine (0.02 mg/kg), once weekly, was started. Three mo later, the lymph glands were not palpable, the bleeding tendency had disappeared, and the platelet count was 120×10^9 /liter. Her condition has remained satisfactory. A causative role of immunosuppressive therapy in the development of the sarcoma seems plausible. (25 refs.)

PATHOGENESIS

See also:

See also

* (Rev.): 77-0605, 77-0610, 77-0611, 77-0613, 77-0638, 77-0639, 77-0641, 77-0660, 77-0662, 77-0670, 77-0679, 77-0680, 77-0681, 77-0684, 77-0694, 77-0703, 77-0710, 77-0715, 77-0717, 77-0718, 77-0719, 77-0720, 77-0721, 77-0722, 77-0724, 77-0725, 77-0726, 77-0727, 77-0728, 77-0729, 77-0730, 77-0731, 77-0732, 77-0733, 77-0734, 77-0735, 77-0736, 77-0739, 77-0740, 77-0741, 77-0742, 77-0743, 77-0744, 77-0745, 77-0746, 77-0747, 77-0748, 77-0749, 77-0750, 77-0751, 77-0753, 77-0754, 77-0756, 77-0757, 77-0759, 77-0766, 77-0767.

* (Chem.): 77-0773, 77-0779, 77-0783, 77-0790, 77-0800, 77-0805, 77-0831, 77-0835, 77-0848, 77-0851, 77-0854.

* (Phys.): 77-0856, 77-0857, 77-0858, 77-0862, 77-0869.

* (Viral): 77-0904, 77-0932, 77-0960.

* (Immun.): 77-1001, 77-1003, 77-1019, 77-1028, 77-1033, 77-1037.

* (Epid.-Biom.): 77-1139, 77-1140, 77-1142, 77-1144, 77-1147, 77-1148, 77-1149, 77-1150, 77-1159, 77-1164.

EPIDEMIOLOGY AND BIOMETRY

- 77-1132 **Cancer Statistics, 1977.** (Eng.) Silverberg, E. (Dept. Epidemiology and Statistics, American Cancer Society, New York, NY) *CA* 27(1): 27-41; 1977.

Estimates of cancer incidence from the National Cancer Institute's Third National Cancer Survey (1969-1971) are presented. Cancer was the second leading cause of death (18.6% of total) in 1974. The site of greatest incidence was breast (20%) for women, and lung (33%) for men; these are estimates for 1977. The survey data indicate that previous estimates of nonmelanoma skin cancer may have been substantially low, and that the incidence is about 300,000 cases annually. (no refs.)

- 77-1133 **The Psychosocial Epidemiology of Cancer.** (Eng.) Fox, B. H. In: *Cancer: The Behavioral Dimensions*. Cullen, J. W.; Fox, B. H.; Isom, R. N., eds. (New York: Raven Press): pp. 11-21; 1976.

Social and personal characteristics and behavior as conditions associated with higher and lower risk of cancer and its consequences are discussed. Many of these conditions and behaviors and their range of confidence with respect to both increased or decreased risk for cancer are tabulated, along with the associated site. It is believed that schistosomiasis among Egyptian farm laborers produces a high risk of bladder cancer. The damming of the Nile, which caused an increase in schistosomiasis, may have increased the risk of bladder cancer. The relaxation of sexual mores may lead to an increased risk of cervical cancer, as early sexual experience and multiple partners can cause cervical erosion. This erosion is associated with greater risk of cancer. It is suggested that a public information program be undertaken to educate the public in the prevention of cancer and not just in its detection. A team including a psychosocial epidemiologist, economist, health systems planner, public health educator, medical education specialist, union health administrator, and relevant others should be formed. The purpose of this team would be to evaluate the effects of various behavior changes on the incidence and mortality associated with the various types of cancer and to study the possibilities of bringing about these behavior changes. (42 refs.)

- 77-1134 **Feasibility of Undertaking Cancer Incidence Studies in Rural Areas of India.** (Eng.) Jayant, K. (Epidemiology Div., Cancer Res. Inst., Tata Memorial

Centre, Parel, Bombay 400 012, India) Potdar, G. G.; Paymaster, J. C.; Sanghvi, L. D.; Sirsat, M. V.; Gangadharan, P.; Jussawalla, D. J. *Bull WHO* 54(1): 11-18; 1976.

Cancer incidence rates in a rural area of India were analyzed by a method involving the use of paramedical personnel for initial screening. Alibag Subdistrict, Kolaba District, State of Maharashtra, with a population of over 100,000, was selected for the study. A total of 37,932 men and 41,413 women from 91 villages were followed up for 1-3 yr. A multistage approach was followed, with trained paramedical staff visiting the individual households for the initial screening. The households were revisited by the investigators 1, 2, and 3 yr later, to ascertain the health status of those enrolled and to register any new cancer cases. The number, type, and diagnostic details of the 132 cancer cases detected at the initial and follow-up visits were determined. In men, 39 new cases were found in 90,422 person-years (a crude av annual incidence of 43/100,000). The most common type of cancer was that of the buccal cavity, with an av annual incidence of 11/100,000. In women, 40 new cases were found, corresponding to 100,232 person-years (av annual incidence of 40/100,000). The age-adjusted incidence was 48/100,000. The most common type of cancer was that of the cervix uteri, with an av annual incidence of 12/100,000. The numbers of cases of cancer of the buccal cavity and pharynx observed in men and in women did not differ from those expected. The observed number of cases of cancer of the digestive system was significantly low in both men and women. In men, there was a highly significant difference between the observed and expected incidences of respiratory system cancer, but not in women. Taking all sites together, the rural incidence rates of 43/100,000 for men and 40/100,000 for women were much lower than the corresponding age-adjusted urban rates of 87.2 and 88.0, respectively. The method can be used for registering common cancer sites in an area where conventional methods are not applicable. (6 refs.)

- 77-1135 **A Method of Estimating Risk for Occupational Factors Using Multiple Data Sources: The Newfoundland Lip Cancer Study.** (Eng.) Chambers, L. W. (Div. Community Medicine, Health Sciences Complex, Memorial Univ. Newfoundland, St. John's Newfoundland, Canada) Spitzer, W. O. *Am J Public Health* 67(2): 176-179; 1977.

The use of national census data, a government cancer registry, hospital patient charts, and a household questionnaire survey to estimate the risk of a cancer associated with an

occupation (commercial fishing) is described. The household survey was considered the only feasible way to test an association of lip cancer with commercial fishing. The survey population consisted of 339 patients with lip cancer, 194 with oral cavity or skin cancer, and 199 controls matched for age, sex and geographic location. The assessment of fishing as a factor in developing lip cancer was published elsewhere. This study indicates that the following information is needed to assess occupation as a risk factor for cancer: 1) all the occupations of the respondent; 2) the time spent in each job; 3) the occupation at the time of the interview. The results from a single occupation question should be used with caution in studies of occupation-related risk. (4 refs.)

77-1136 Frequency and Treatment of Reticulum Cell Sarcoma and Survival Time of the Patients in the German Democratic Republic. (Ger.) Herold, H. J. (Zentralinstitut für Geschwulststatistik, DDR-1197 Berlin, Stern-damm 13, E. Germany) Wolf, M.; Staneczek, W. *Zentralbl Chir* 101(25): 1537-1550; 1976.

Between 1960 and 1973, 7,467 reticulum cell sarcomas were recorded in a register of carcinoma patients. The distribution of age, sex, size and frequency during the different years and districts are discussed along with the problems of confirming the diagnosis and histological findings. The 5-yr survival rate for reticulum cell sarcoma patients was 16.0% and the 10-yr rate was 10.3%; these rates are correlated to therapy, age, and size of the tumor. (25 refs.)

77-1137 Epidemiological Aspects of Chronic Myeloid Leukemia. (Eng.) Plotnikov, I. K. (First Dept. Hospital Therapy, D. I. Ulianov Kuibyshev Medical Inst., Kuibyshev, USSR) *Probl Gematol Pereliv Krovi* 21(11): 29-33; 1976.

The occurrence of chronic myeloid leukemia (CML) in the Kuibyshev District (USSR) is reviewed. From 1965 to 1972, CML was diagnosed in 202 patients (97 men, 105 women, aged 14-75 yr). The overall morbidity index was 0.93; the incidence of the disease was 2.1-2.7 times higher among elderly men (age group 60-69 yr). Different exogenous and endogenous factors were related to the incidences of CML. Fifty-three patients had a history of malaria and infectious hepatitis, compared to 25/160 controls (patients with Stage II hypertension). The incidence of leukemia and malignant tumors was 2 times higher among the parents and sibs of the CML patients than among the relatives of the controls ($p < 0.005$). (12 refs.)

77-1138 Cancer Epidemiology: A Continuing Series on Different Sites, Based on the New South Wales Data. Series No. 3: Colon and Rectal Cancer in NSW. (Eng.) Ford, J. (Central Cancer Registry, Health Commission New South Wales, New South Wales, Australia) *Cancer Forum* 9: 199-203; 1976.

The 1972 statistics for the occurrence of new cases of colon and rectal cancer in New South Wales were collated. Malignant tumors of the appendix and unspecified tumors of the intestinal tract plus carcinoid tumors and villous adenoma were included in the total of 1,469 cases. Tumors of the rectosigmoid junction were coded to cancers of the rectum. Colorectal cancer was the second commonest cancer in men and women, after lung and breast cancer, respectively. The new cases of colorectal cancer were determined by sex and by two age groups, excluding unspecified tumors of the intestinal tract. Over 80% of the new cases occurred in persons > 50 yr. A dissection of the age-specific crude incidence rates per 100,000 demonstrated a steep rise in incidence with increasing age in colorectal cancers for both sexes. The incidence rate of colon cancer in both sexes was very similar at all ages, but rectal cancer in men increased at a much faster rate than that in women, so that after 60 yr, the male rate was approx double that for females. Major operative procedures, such as colectomy, excision of lesions of the colon and rectum, and abdominoperineal resection, were carried out for 985 of the 1,469 new cases. A plea is made for greater specificity of primary sites of cancers on the New South Wales notification forms. (no refs.)

77-1139 Cancer of the Large Bowel in the African: A 15-Year Survey at Kinshasa University Hospital, Zaire. (Eng.) Kenda, J. F. (Dept. Surgery, Unit Abdominal General Surgery, Univ. Hosp., Kinshasa, Zaire) *Br J Surg* 63(12): 966-968; 1976.

A total of 954 solid cancers were recorded within a 15-yr period at Kinshasa University Hospital, 46 in the colon, rectum, and anal canal. There were 36 men and 10 women ranging in age from 19 to > 60 yr, with some predilection for the third and fourth decades. The average age was 35 yr, and 20/46 patients were below this limit. The primary tumor sites were rectum (23), cecum (8), ascending colon (4), transverse colon and flexures (2), descending and sigmoid colon (5), and anal rectum (5). The most commonly reported symptoms, such as constipation, wt loss, abdominal pain, weakness, rectal bleeding and anemia, were seen in the older patients. In the group of seven patients with intestinal obstruction, five were < 35 yr old. The histopathology, obtained for 38 tumors, was: adenocarcinoma (30), epidermoid carcinoma (4), sarcoma (1), lymphoma (1), carcinoma in situ (1), and atypical carcinoma (1). Eight of the 30 adenocarcinomas were colloid or mucous carcinomas. There was nothing to suggest any known predisposing condition such as ulcerative colitis or

familial polyposis. Intestinal amebiasis was associated with cancer in three patients. The incidence of cancer of the large bowel in young Africans is higher than in Western countries, the clinical presentation in young patients is often unusual, and the incidence of mucous carcinoma tends to be higher. (15 refs.)

- 77-1140 Carcinoma of the Stomach in Rhodesian Africans and a Comparative Review.** (Eng.) Dent, R. I. (Godfrey Huggins Sch. Medicine, Univ. Rhodesia, Salisbury, Rhodesia) Fleming, J. B.; Wicks, A. C. *Clin Oncol* 3(1): 17-26; 1977.

The results of an 8-yr study of gastric carcinoma in Rhodesia are presented. Of the 158 patients with histologically proven carcinoma of the stomach, 42% were urban dwellers, all were black, and the male to female ratio was 2.8:1. No statistical trend was seen according to socioeconomic status of 51 male patients. The patient symptoms were pain (85%), weight loss (80%), vomiting (75%), haematemesis (30%), and anorexia (23%). The blood group distribution in this study was the same as the distribution in a normal hospital population. Resection of the tumor was performed on 53 of the 120 patients who underwent laparotomy; however, in 25 of the resected group, the measure was palliative only. The mortality rate following resection was 15%; 29% of all patients died while in the hospital. After the immediate post-operative period, no accurate mortality rates could be calculated, since there was only a 50% follow-up rate. Carcinoma of the stomach was the fifth commonest malignancy seen at the hospital. It is suggested that in this population the increased incidence of gastric carcinoma, previously considered rare in black Africans, may result from a transition toward a European life-style. (34 refs.)

- 77-1141 Geographic Correlation Between the Occurrence of Endemic Nephropathy and Urinary Tract Tumours in Vratza District, Bulgaria.** (Eng.) Chernozemsky, I. N. (Inst. Oncology, Medical Acad., 1156 Sofia, Vratza, Bulgaria) Stoyanov, I. S.; Petkova-Bocharova, T. K.; Nicolov, I. G.; Draganov, I. V.; Stoichev, I. I.; Tanchev, Y.; Naidenov, D.; Kalcheva, N. D. *Int J Cancer* 19(1): 1-11; 1977.

The first reports on endemic nephropathy (EN) in Bulgaria appeared in 1952-1956. It is now generally accepted that EN is a fatal kidney disease encountered only in certain rural areas of Bulgaria, Yugoslavia and Rumania. Data on the occurrence of endemic nephropathy (EN) and urinary tract and other cancers in an endemic region of Vratza district, Bulgaria, for 1965-1974, are presented. In endemic villages studied (19) a high incidence of urinary tract tumors, affecting

in particular the renal pelvis and ureter, closely correlated with the EN incidence and mortality rates. In the villages with high and moderate EN incidences urinary tract tumors are the most common neoplasms. They account for 25% of all tumor sites in males and 30% in females. In hyperendemic villages age-adjusted incidences of EN and urinary tract tumor were 506/10⁵ and 104/10⁵ in females, and 315/10⁵ and 89/10⁵ in males, respectively. EN mortality in these villages accounted for over 40% of all deaths in females and about 30% in males. Females and middle-aged persons were most often affected. Urinary tract neoplasms were often multiple and nearly 90% of them originated in the uro-epithelium. In endemic and non-endemic villages (8) of the region studied the frequency and pattern of nonurinary tract cancers were similar, with statistical values close to those of the rural population of Vratza District and Bulgaria as a whole. The striking parallels between EN and uroepithelial neoplasms (similar geographic, age, and sex clustering) require further study. (36 refs.)

- 77-1142 Carcinoma In Situ of the Larynx.** (Eng.) Doyle, P. J. (Div. Otolaryngology, Univ. British Columbia, 865 West 10th Ave., Vancouver, British Columbia, Canada) Flores, A.; Douglas, G. S. *Laryngoscope* 87(3): 310-316; 1977.

A retrospective survey of laryngeal carcinoma in situ (CIS) was presented. In the 32-yr period under review (1940-1972) there were 38,818 cancer patients, including 586 with invasive laryngeal carcinoma and 43 with CIS. The increased incidence in recent years is only apparent, dependent on more accurate tissue excision and more precise biopsy specimens. There were 143 cases of abnormal associated histology, 20 associated CIS cases, and 26 leukoplakic cases in the 586 patients with frank carcinoma. Of the group of 143 patients, 74 were under observation before the diagnosis of invasive carcinoma; 4 of these had CIS and 29 had "pre-malignant" disease. In 54% of all patients with suspected laryngeal changes, 1 yr was required before invasive carcinoma could be identified. The most frequent signs of laryngeal modification were associated chronic inflammation and leukoplakia, followed by dysplasia and polyps, papilloma, CIS, various keratoses, and benign nodulation. (7 refs.)

- 77-1143 Benign Bone Tumors. Statistical Survey.** (Fre.) Faure, C. (Service de Radiologie, Hopital Trouseau, 8 a 28, avenue du Dr Arnold-Netter, F 75571 Paris Cedex 12, France) *J Radiol Electrol Med Nucl* 57(8/9): 621-623; 1976.

A survey of benign bone tumors in 1,031 children and 647 adults is presented. Results are tabulated according to tissue of origin (fibrous, cartilaginous, osseous, cardiovascular,

etc.), and, in the children, according to age. Osteochondromas (28.2%), simple osseous cysts (21.5%), and nonossifying fibroma (15.1%) are the most frequently observed benign bone tumors in children. The incidence of primary malignant bone tumors in children is estimated to be 9.7%. (1 refs.)

- 77-1144 Skeletal Distribution of Chondroblastomas. Relationship with Areas of Ossification.** (Fre.) Le Sec, G. (No affiliation given) Forest, M.; Abelanet, R.; Nezelof, C. *J Radiol Electrol Med Nucl* 57(8/9): 623-625; 1976.

The benign bone tumor, chondroblastoma, is not readily recognized by clinicians, radiologists, and pathologists, and its frequency is probably underestimated. Large clinical centers report the incidence as <1% of the total of benign and malignant bone tumors; however, since 1968 the number of literature cases has been increasing. Of 219 cases reported, 82% were between 10 and 30 yr of age (median 17 yr). The most likely sites, as reported in a series of 458 cases, are the distal femur (16%), the proximal humerus (22%), the proximal femur (15.2%), and the proximal tibia (14.8%). Apparently, the chondroblastoma is associated with ossification centers during the growth period. Radiologically, the chondroblastoma shows a limited area of osteolysis, 3-6 cm in diameter, generally located eccentrically on the epiphysis. The lacunar zone is typically traversed by a network punctuated by small areas representing intratumoral calcification. The age of the patient and the rapid growth of the tumor may confuse the diagnosis with that of malignant tumor. (9 refs.)

- 77-1145 Cancer Mortality Among Japanese in Hawaii. Comparison of Observed and Expected Rates Based on Prefecture-of-Origin in Japan.** (Eng.) Nomura, A. (Sch. Public Health, Univ. Hawaii, 1960 East-West Road, Biomedical Science Building D-102, Honolulu, Hawaii 96822) Hirohata, T. *Hawaii Med J* 35(10): 293-297; 1976.

Using the Japanese national cancer mortality rates as standard, a computation was made of standardized mortality ratios, specific for site and sex, based on the Japanese prefectures from which the majority of Hawaiian Japanese originated. The observed versus expected mortality per 100,000 among Hawaiian Japanese for stomach cancer was 0.70 for men, and 0.63 for women. However, some ratios were higher than one: breast (females 1.51), buccal cavity and pharynx (males 1.59; females 2.00), large intestine (males 3.81; females 1.88). The magnitude and consistency of the decrease in stomach cancer of Japanese living in Hawaii compared to those in Japan indicate that this decrease is genuine. Thus environment seems to be important in the etiology of stomach cancer. (29 refs.)

- 77-1146 Detection of Gastric Cancer in Patients Prophylactically Examined for Achlorhydric Gastritis.** (Rus.) Drugova, T. A. (Dept. Epidemiology Malignant Tumors, Scientific Center Oncology, Moscow, USSR) *Klin Med (Mosk)* 54(10): 60-63; 1976.

The efficacy of annual prophylactic examinations of chronic achlorhydric gastritis patients for the early detection of gastric cancer was evaluated by questionnaires sent to 109 therapists. Each therapist treated an average of 10 patients with achlorhydric gastritis. Gastric cancer was detected in a total of 53 patients. In spite of the 2.6-fold increase in gastric cancer morbidity in this group compared to that in the general population, the detection rate was still low. It was concluded that the objective of these annual examinations should be treatment of the gastritis and not detection of gastric cancer. (19 refs.)

- 77-1147 Association of Carcinoma with Congenital Cystic Conditions of the Liver and Bile Ducts.** (Eng.) Bloustein, P. A. (Dept. Pathology, Univ. Colorado Sch. Medicine, 4200 E. Ninth Ave., Denver, CO 80220) *Am J Gastroenterol* 67(1): 40-46; 1977.

Reported cases of carcinoma associated with congenital cystic conditions of the liver and bile ducts are tabulated with respect to the specific type of congenital abnormality. The frequency with which the epithelium of Meyenburg complexes and of intrahepatic congenital cysts, either solitary or multiple, undergoes malignant transformation is very slight. The association between malignancy and congenital hepatic fibrosis is also relatively rare, occurring with a frequency of 1.3%. The incidence of carcinoma is 4% in cases of choledochal cyst and 7% in congenital cystic dilatation of the intrahepatic bile ducts. Those congenital conditions in which the epithelium is in contact with the biliary flow appear to have a higher risk of malignant transformation than do solitary cysts or the cysts of polycystic liver disease, suggesting that something in the bile may be carcinogenic or may potentiate a neoplastic change. (42 refs.)

- 77-1148 Familial Hyperparathyroidism (Letter to Editor).** (Eng.) Christensson, T. (Dept. Medicine, Serafimerlasarettet, S-112 83 Stockholm, Sweden) *Ann Intern Med* 85(5): 614-615; 1976.

The prevalence of familial primary hyperparathyroidism in Stockholm, Sweden, was studied. Between 1971 and 1973, 15,903 persons (aged 20-63 yr) took part in a medical screening program. A total of 95 (80 women, 15 men) was found to have verified hypercalcemia. In 82/95 patients, causes of

hypercalcemic disorders other than primary hyperparathyroidism were ruled out. So far, 60 of these patients have been operated on, and parathyroid adenomas have been found in all but 2. The diagnosis in the remaining 22 patients is probably primary hyperparathyroidism. Parents, siblings, and children of each of the 82 patients were invited to participate in further studies. Eighty-six of 90 parents took part in a follow-up study from 1973-1976, as did 150/162 siblings and 148/156 children of the subjects with verified hypercalcemia. All subjects underwent repeated serum calcium, serum phosphate, serum albumin, serum magnesium, and creatinine clearance determinations. Other cases of primary hyperparathyroidism were found in members of only two of the investigated families. In family no. 1, two cases were found, but family no. 2 had eight cases covering three generations. No other endocrine disorders were detected in the family members. There were no laboratory manifestations except for the repeatedly confirmed elevation of serum calcium. The prevalence of primary hyperparathyroidism was higher in the health-screened Swedish population (0.52%), compared to corresponding figures from American studies. However, the frequency of familial primary hyperparathyroidism in this Swedish population (0.12/1,000) does not differ from corresponding data in American surveys. (5 refs.)

77-1149 A Small Cluster of Hodgkin's Disease. (Eng.) Evans, A. R. (Sheffield Area Health Authority, Sheffield, England) Hancock, B. W.; Brown, M. J.; Richmond, J. *Br Med J* 1(6068): 1056-1057; 1977.

A cluster of nine cases of Hodgkin's disease and one case of lymphoblastic leukemia in an area of < 1 square kilometer was investigated. All patients presented within a 4-yr period. The incidence in this area during this time was 15 times the expected incidence. No definite patient-to-patient contacts were established despite the fact that several of the patients lived near one another. No contacts common to all the patients before the onset of the disease were found. Clinical, social, and drug histories did not appear to be relevant. None of the patients were related, and immune status was normal in the patients tested. The close relatives of the patients showed an increased incidence of malignant neoplasms when compared to the relatives of age- and sex-matched controls. Studies are in progress to determine if environmental, geographical, climatic, and entomological factors may have influenced the incidence of Hodgkin's disease in this area. (19 refs.)

77-1150 Primary Carcinoma and Carcinomatous Disease. (Fre.) Gorlina, A. (Laboratoire Central d'Investigation Scientifique, Ministere de la Sante, Moscow, USSR) Kossarev, V. *Ann Otolaryngol Chir Cervicofac* 93(12): 737-741; 1976.

In the period 1961-1975, 155 patients (60 men, 95 women) with multiple primary neoplasms were observed at a general hospital in Moscow. Two neoplasms were present in 138 (three in 12, and in 5 patients, there were more than four primary sites. The frequency of multiple neoplasm cases was 3.4% of the total neoplasm cases from 1961 to 1971; the frequency increased to 7.6% in the remaining 5 yr. Other authors have reported frequencies ranging from 0.3% to 8%. The increase of multiple primary tumors can be attributed to improved diagnoses and a longer life span. Tabulation of the sites of multiple tumors shows the order of frequency to be breast, skin, digestive system, respiratory system, and hematopoietic system. The sites are most likely to occur in paired organs or in the same organ system, as was observed in 22 cases. It is often difficult to distinguish a second or third primary neoplasm from a metastasis. (9 refs.)

77-1151 Immunologic Factors in Childhood Cancer. (Eng.) South, M. A. In: *Trends in Childhood Cancers. Proceedings of the Fifth Annual Symposium of the Division of Oncology of The Children's Hospital of Philadelphia and the Department of Radiation Therapy of The American Oncologic Hospital of the Fox Chase Cancer Center.* Donaldson, M. H.; Seydel, H. G., eds. (New York: John Wiley & Sons): pp. 23-29; 1976.

The association between immunologic factors in oncogenesis in children and the immune status of the child during cancer treatment was examined. Of 198 tumors reported to the Registry for Cancer in Immune Deficient Patients, 111 were in children under 15, and lymphoreticular malignancies were the most common tumor type. According to figures from a kidney transplant registry, the calculated relative risk of tumors in people who have transplants as children under 20 is increased 44 times for lymphomas and 9 times for other kinds of tumors. The most plausible explanation for the increased incidence of lymphoreticular malignancies in these two groups seems to be immunosuppression with concurrent immunostimulation. Secondary immune defects produced by therapy affect both the B- and T-cell systems. The immunosuppressive effects of drugs used in cancer chemotherapy are long-lasting, and the slow and gradual return of immune capabilities after therapy results in many infectious deaths during remission. These immune defects, however, are transient in patients who have effective therapy against their malignancies, indicating that extremely aggressive antimicrobial therapy is necessary in patients with malignancies who have a chance for cure. (no refs.)

77-1152 Previous Pregnancy as a Protective Factor Against Death from Melanoma. (Eng.) Hersey, P. (Kanematsu Memorial Inst., Sydney Hosp., Sydney, New

outh Wales 2000, Australia) Stone, D. E.; Morgan, G.; McCarthy, W. H.; Milton, G. W. *Lancet* 1(8009): 451-452; 1977.

The case records of 443 consecutive female patients admitted to the Melanoma Unit at Sydney Hospital over the period 1961-1971 were examined for information on the number of pregnancies before melanoma developed, age at presentation, clinical stage of melanoma at presentation, time to recurrence, and death from melanoma. The relevant data for women with or without pregnancies before melanoma developed were collected. There were approx equal numbers of patients with melanoma Stages 1, 2, and 3 in both groups. There was slight preponderance of women < 50-yr-old among those without previous pregnancies. The main difference in age distribution between the two groups was the absence of a peak incidence in the fourth and fifth decades in the group without previous pregnancies. Five-year survival rates were significantly different between those with (77%) and without (8%) previous pregnancies. Analysis of the survival period in terms of age (arbitrarily chosen above or below 50) in women with or without a previous pregnancy was performed. The difference between the two groups was most pronounced in those > 50 compared with those < 50. However, the prognosis in both groups was much better for those < 50 than in those > 50. In the < 50 group, the 5-yr survival rate was 83% in women with a previous pregnancy and 73% in those without a previous pregnancy, compared with 73% and 53%, respectively, for women > 50. The effect of the stage of melanoma at presentation was also evaluated. Differences between women with and without previous pregnancies were apparent irrespective of the stage, although the differences were not statistically significant. The 5-yr survival rate for women with Stage 1 melanoma with previous pregnancies was 84% compared with 75% for those with no previous pregnancies. Comparable 5-yr survival rates for patients presenting with Stage 2 or 3 melanoma were 38% and 29%, respectively. The results may indicate that the immune response to tumors is significant not in preventing their occurrence, but in preventing dissemination of melanoma cells and death from the tumor. (11 refs.)

77-1153 **Cervical Carcinoma in Zambia.** (Eng.) Naik, K. G. (Dept. Pathology Microbiology, Sch. Medicine, Univ. Zambia, PO Box RW 110, Lusaka, Zambia) *Int J Gynecol Oncol* 62(2): 110-111; 1977.

A series of 274 cases of cervical carcinoma in Zambian Africans was examined. Most of the patients were 30-59 yr old. Cervical carcinoma was the most common malignant tumor, constituting 29.3% of all female cancers and 12.5% of all malignancies. Poorly differentiated squamous cell carcinoma (2.25%) was the most common subtype. Concomitant bilharziasis was noted in 67 of the cases. In a subseries of 59 women, 12 reported first coitus before age 15, 42 before age 20, and 55 before age 20. Early marriage was more frequent

among patients with cervical carcinoma. Most (85%) of the patients had married by the age of 20. A high proportion of the patients reported pregnancy at an early age: 61% had their first pregnancy before age 18 and 75% before age 21. Most Zambian men (96%) are uncircumcised, and they have a low incidence of penile carcinoma. No correlation was noted between cervical carcinoma and circumcision. (17 refs.)

77-1154 **Changes in the Incidence of Squamous Cell Carcinoma and Adenocarcinoma of the Uterus in Perugia During the Period 1942-1976.** (Ita.) Maltzef, N. (Universita degli Studi Perugia, Divisione di Ricerche sul Cancro, Perugia, Italy) *Lav Ist Anat Istol Patol Perugia* 36(3): 93-107; 1976.

A series of 1,848 uterine cancer biopsies was collected at the Institute of Pathological Anatomy and Histology in Perugia from 1942 to 1976. The material was classified as squamous cell carcinoma or adenocarcinoma and subdivided into 5-yr periods. There was a progressive decrease in the incidence of squamous cell carcinoma from 86.9% in 1947-1951 to 37% in 1972-1976. Endometrial adenocarcinoma increased from 11.9% in 1947-1951 to 58.2% in 1972-1976. There were no changes in the incidence of cervical adenocarcinoma. As most cancer biopsies in the Umbrian region are registered at the Institute in Perugia, data relevant to the population of women in Umbria were taken from 1951-1971 censuses and analyzed from 1947-1956 and 1967-1976. The age-adjusted rates from 1951-1971 indicate a 171% increase in the incidence of adenocarcinoma and a 24% decrease in the incidence of squamous cell carcinoma. The increase in adenocarcinomas is in part attributable to progressive aging; from 1951 to 1971, the number of women under 20 decreased by 19.4% and the high risk uterine cancer population increased by 5.3%. The increasing use of estrogens by postmenopausal women may also be a contributing factor. The decrease in squamous cell carcinoma is probably due to the increased application of methods to detect preclinical lesions. (19 refs.)

77-1155 **Trends in Mortality from Uterine Cancer in Relation to Mass Screening.** (Eng.) Christopher, W. M. (Dept. Pathology, Univ. Louisville Sch. Medicine, Louisville, KY 40208) *Acta Cytol (Baltimore)* 21(1): 5-9; 1977.

Mortality rates from cancer of the cervix uteri, as well as for all uterine cancer, have shown a remarkable decrease in recent years in Louisville, Kentucky. For women ages 30-39 the decrease was 70.8%, and for ages 50-59, 69%. No change in rates was noted for women ages 70 yr and over. These changes correlate well with the success of recruitment for

screening of women, according to age. The high degree of success in screening the low socioeconomic quartile is thought to be of prime importance. The average, annual, age-adjusted mortality for uterine cancer other than cervix also fell impressively. In contrast to Louisville, mortality from cervical cancer in England and Wales, with the exception of the younger age group, has remained fairly constant over the past decade. Denmark showed no mortality decline between 1961 and 1971. Like England and Wales and unlike Louisville, screening there had not achieved high population coverage. In the absence of a comparable decrease in an unscreened population, it appears that the observed mortality decline is dependent on screening for cervical cancer. (16 refs.)

- 77-1156 **Cancer of the Uterus: Mortality Trends Since 1950.** (Eng.) Hill, G. B. (Health Div., Statistics Canada, Ottawa, Canada) *S Afr Cancer Bull* 20(3): 96-105; 1976.

The mortality trends of cancer of the uterus since 1950 are evaluated based on data assembled by the World Health Organization. During the 1960s, a significant fall in mortality from cancer of the cervix at ages 35-64 yr certainly occurred in Canada, New Zealand, and Norway. It probably occurred in Australia, Portugal, Switzerland, and the United States, while it possibly occurred in Austria, Belgium, Czechoslovakia, Finland, France, Hungary, Israel, Japan, Northern Ireland, and Scotland. It probably did not occur in Chile, Denmark, England and Wales, Federal Republic of Germany, Ireland, Italy, Netherlands, Sweden and Venezuela. During the decade between 1955-1959 and 1965-1969, mortality from cancer of the cervix fell significantly in certain countries, including Canada and the United States, where screening was first introduced on a large scale. Screening reduced the mortality by detecting and eradicating carcinoma in situ and by diagnosing invasive cancer in its early stages when treatment is more effective. There was a downward trend in the mortality rate for uterine cancer as a whole. The most significant risk factors found in etiological studies of cancer of the cervix are early sexual intercourse and promiscuity. It is possible that increased bathing by both sexes, resulting in better genital hygiene, has reduced the risk of an infective agent being transmitted. Other possible factors are the more effective treatment of cervical infections and the increased recourse to hysterectomy for benign uterine conditions. Apart from the decreased incidence, the fall in mortality could be due to more effective treatment of invasive cancer. The geographic distribution of mortality from choriocarcinoma is in keeping with the clinical finding that the disease is more common in Asia. (35 refs.)

- 77-1157 **Preliminary Results from a Mass Screening Program for Breast and Uterine Cancer.** (Cro.)

Ribaric, M. (Sluzba za Zdravstvenu Zastitu Zena Zavoda za Zastitu Zdravlja Grada Zagreba, 41000 Zagreb, Yugoslavia) *Stojiljkovic, C. Libri Oncol* 5(1): 37-40; 1976.

Preliminary results from a mass screening program for breast and uterine cancer in women between 30 and 49 yr of age are given. It was found that approx 10% of the women had no previous gynecological checkup; of the 1,410 women who went through the program, cytological findings were negative in 1,386, 18 were suspected of malignancy and 6 were found with malignant lesions; and 65 women were either hospitalized or sent for further testing. The following conclusion were made: (1) an early discovery of malignant lesions offer good chances for total recovery; (2) systematic screening reveals many benign changes in the breast and genitals that can be treated immediately; (3) mass screening programs reach women who otherwise might not see a doctor; (4) making and maintaining contacts with various health and social organizations encourages the preventive aspects of health work; and (5) a uniform approach in diagnosing and treating breast and uterine cancer raises the professional level of the medical personnel. (3 refs.)

- 77-1158 **Are Breast Patterns a Risk Index for Breast Cancer? A Reappraisal.** (Eng.) Mendell, L. (Dept. Radiology, Jewish General Hosp., Montreal, Canada) *Rosenbloom, M.; Naimark, A. Am J Roentgenol* 128(4): 547-1977.

The theory that xeromammographic breast patterns can be used as a risk index for breast cancer was tested in retrospective study. The material consisted of 162 patients, seen over a 4-yr period, with pathologically proved breast cancer who had xerograms prior to surgery. Xerograms were classified according to the criteria used in the study on which the theory under consideration was based. The criteria were as follows: N1, lowest risk, parenchyma composed primarily of fat with small amount of dysplasia and no ducts visible; P1, low risk, parenchyma chiefly fat with prominent ducts up to one-fourth of breast volume; P2, high risk, severe involvement with prominent duct pattern; and DY, highest risk, severe involvement with dysplasia. In the previous study, six times as many patients with breast cancer appeared in the P2 and DY groups compared to the N1 and P1 groups; in the present study, the ratio was 1.5:1. It is concluded that an inherent bias in the design of the original study led to erroneous conclusions and that the breast remains an organ at relatively high risk for cancer regardless of breast pattern. (2 refs.)

- 77-1159 **Chronic Mastitis and Carcinoma of Breast (Letter to Editor).** (Eng.) Martin, S. P. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033) *Mack, T. M. Lancet* 1(8015): 805; 1977.

radiation exposure must be taken into account when considering the association between breast cancer and chronic mastitis. Emphasis is made of the fact that chronic mastitis has often been treated with x-rays. Therefore, information on radiation exposure as well as chronic cystic mastitis should be made available before the influence of either on the risk of breast cancer can be measured. (19 refs.)

- 77-1160 **Problems of High-Risk Populations and High-Risk Nonresponders: Smoking Behavior.** (Eng.) Hewchuck, L. A. In: *Cancer: The Behavioral Dimensions*. Gullen, J. W.; Fox, B. H.; Isom, R. N., eds. (New York: Raven Press): pp. 93-99; 1976.

Programs and methods for helping the smoker who wants to quit are discussed. Smokers seeking aid in quitting have no way of knowing what type of treatment they require and how extensive it must be. Most smokers are not aware that there are a number of approaches to smoking cessation. To identify what individual and what method will be successful, information on demographic data, attitudes toward health and smoking, personality correlates, and smoking behavior are being gathered. There are three broad categories of treatment. Level I can be applied to those who are or are not motivated to stop smoking. It consists of a short message by a physician presented in the framework of the doctor-patient relationship. The goal is to make the patient aware that smoking is an important problem that has personal meaning or relevance. Level II includes the use of audio and written material helping the smoker to quit. This is applied to smokers who are motivated enough to seek assistance. The patients are required to master the step-by-step procedure on their own. Level III provides a structured procedure and the additional support of a therapist or a group of persons who are also trying to quit smoking. This level is for those who need a structure-support system. A detailed discussion of level III results is presented. (22 refs.)

- 77-1161 **Lung Cancer Incidence in Cigarette Smokers: Further Analysis of Doll and Hill's Data for British Physicians.** (Eng.) Whittemore, A. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY 10016) *Biometrics* 32(4): 805-816; 1976.

An investigation of the lung cancer incidence in cigarette smokers, Doll's and Hill's data for British physicians are further analyzed. Both the Weibull and lognormal distributions approximated the data equally well in the given time and dose ranges. The data were consistent with Doll's conclusion that man risk was proportional to dose rate and inconsistent

with mouse skin painting experiments in which incidence was proportional to the square of dose rate. The relatively low incidence at high doses and durations could be an artifact due to the same incompleteness of data that was reported to affect those over 80 yr of age. On the other hand, it could be due to cell toxicity at higher smoking rates. It pointed to either a higher value of K_2 at the lower doses, or else, at higher doses, to a time delay before tumors could appear, indicating that heavier smoking somehow decelerated progression toward tumor. If K_2 increased as dose decreased, then at very low doses the consequences of the model would be modified. In particular, there would be a higher probability of cancer and a later average cancer time among cancer cases. The probability of cancer at a given low dose was lower for the lognormal model than for the Weibull model. According to the lognormal model, the average age of cancer increased as dose decreased. However, it remained independent of dose according to the fitted Weibull distribution. If the noted trend to increasing upward concavity as dose rate decreases is significant, the Weibull distribution will become a better approximation than the lognormal distribution. (13 refs.)

- 77-1162 **Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors.** (Eng.) Doll, R. (Dept. Regius, Radcliffe Infirmary, Oxford OX2 6HE, England) *Br Med J* 2(6051): 1525-1536; 1976.

Mortality in relation to smoking is evaluated. The mortality rates of 34,440 male doctors over the 20 yr from November 1951 to October 1971, both in total and in relation to their smoking habits, were determined. Of the men studied, 10,072 were known to have died before November 1, 1971; 24,265 were known to have been alive at that date; and 103 were not yet traced. The ratio of the death rate among cigarette smokers to that among lifelong nonsmokers of comparable age was, for men over 70 yr, approx 1.5:1, whereas for men under 70 yr it was approx 2:1. Smoking caused death by lung cancer, heart disease, vascular disease, and chronic obstructive lung disease among middle-aged men. For lung cancer, the relative mortality decreased steadily with duration of stopping until more than 15 yr after stopping. However, at this time, the mortality was still double the rate in life-long nonsmokers of similar ages. A separate examination was made of the ex-smokers who had stopped smoking cigarettes before they had reached 30 yr of age. Such men had smoked for an average of 7 yr. Only 57 deaths occurred among them. Their mortality was 53% of that in men of the same age who continued to smoke and 93% of that in nonsmokers. This difference suggested that these men suffered few, or no, deaths due to the 7 yr during which they smoked. Lung cancer and cigarette consumption decreased as the investigation progressed. Thus, there was a causal association between lung cancer and smoking. Much of the excess mortality in cigarette smokers can be attributed to the habit. (49 refs.)

- 77-1163 Reverse Dhumti Smoking in Goa: An Epidemiologic Study of 5,449 Villagers for Oral Precancerous Lesions.** (Eng.) Bhonsle, R. B. (Basic Dental Res. Unit, Tata Inst. Fundamental Res., Homi Bhabha Road, Bombay-400 005, India) Murti, P. R.; Gupta, P. C.; Mehta, F. S. *Indian J Cancer* 13(4): 301-305; 1976.

The prevalence of tobacco habits, with particular emphasis on reverse dhumti smoking and its association with oral cancer and precancerous lesions, was studied in Goa. Dhumti is made by rolling a tobacco leaf inside the leaf of a jackfruit tree; males smoke in the conventional manner but females may also smoke it in a reverse manner keeping the burning end inside the mouth. Using random sampling, 5,449 individuals in 11 villages were examined by dentists in a house-to-house survey. Reverse dhumti smoking was practiced by 0.4% of the sample. Leukoplakia was found in 1.6% of the population, leukokeratosis nicotina palati in 1%, lichen planus in 0.2% and submucous fibrosis in 0.04%. A correlation of various lesions with tobacco habits is tabulated. A marked association was observed between palatal lesions and the habit of reverse dhumti smoking practiced exclusively among Christian females in this study. Among 24 reverse dhumti smokers, 25% had leukokeratosis nicotina palati. The association of other tobacco habits with oral lesions was similar to that reported from other parts of India. (8 refs.)

- 77-1164 A Follow-up Study of Sixty-one Oral Dysplastic Precancerous Lesions in Indian Villagers.** (Eng.) Pindborg, J. J. (Dept. Oral Pathology, Royal Dental Coll., 4, Universitetsparken, DK-2100 Copenhagen O, Denmark) Daftary, D. K.; Mehta, F. S. *Oral Surg Oral Med Oral Pathol* 43(3): 383-390; 1977.

During a 7-yr follow-up study of 61 patients with precancerous epithelial (dysplastic) oral lesions, 6.6% of the lesions developed into carcinoma; 14.8% regressed. Of the 33 persons who had persistent, stationary lesions, 27 were smokers. All of those who developed oral carcinoma, and 8/9 of those whose lesions regressed, used tobacco. (10 refs.)

- 77-1165 A Reanalysis of Leukemia Data on Atomic Bomb Survivors Based on Estimates of Absorbed Dose to Bone Marrow (Meeting Abstract).** (Eng.) Kerr, G. D. (Health Physics Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) Jones, T. D. *Health Physics* 31(6): 568; 1976. (no refs.)

- 77-1166 The Observation and Analysis of Cancer Deaths among Classified Radiation Workers.** (Eng.) Reissland, J. A. (Natl. Radiological Protection Board, Har-

well, Oxon, United Kingdom) Kay, P.; Dolphin, G. W. *Phys Med Biol* 21(6): 903-919; 1976.

The analysis and observation of cancer deaths among classified radiation workers are described. The number of radiation-induced cancer deaths that would occur in a population if the risk were 10^{-4} per rad was determined. A longer latent period allowed a greater influence of the normal death rate and resulted in a smaller number of radiation-attributed deaths. An increase was due to the concentration of the risk into a shorter period, allowing radiation-induced death instead of natural death slightly more frequently. There were 7.7 radiation cancer deaths against a background of 1,406 other cancer deaths in a steady-state population. In a period of 25 yr, one would expect 24 leukemia deaths, of which 0.8 would be radiation-induced. In the same time period, one would expect 1,056 cancer deaths, of which 2 would be radiation-induced. These results would occur in a particular industry employing 3,000 radiation workers each receiving an average dose of 0.5 rad/yr. If a large survey (100,000) on occupational exposure is made, the first conclusions would not be expected for at least 20 yr. If total exposures are much less than 100,000 man rads/yr or if the risk is less than 100 per 10^6 man rads, however, the time necessary to prove a positive effect of radiation on the incidence of deaths from cancer becomes very great, with little prospect of making statistically valid intermediate statements. The lowest detectable values are an order of magnitude larger than those expected for a workforce of 3,000. Only an international or a national survey can produce data adequate for even modest objectives. (7 refs.)

- 77-1167 Occupational Bladder Tumour Cases Identified During Ten Years' Interviewing of Patients.** (Eng.) Davies, J. M. (Inst. Cancer Res., Fulham Road, London SW3 6JB, England) Somerville, S. M.; Wallace, D. M. *Br J Urol* 48(7): 561-566; 1977.

One thousand patients with urothelial tumors seen at the Royal Marsden Hospital during a 10-yr period up to the end of 1975 were interviewed as to the type of jobs they had held. Included were 775 men and 225 women, most of whom were aged 60-79 yr. Department of Health and Social Security (DHSS) benefits are available to those whose bladder cancer can be related to exposure to the following classes of carcinogens: (1) Alpha-naphthylamine or beta-naphthylamine; (2) diphenyl substituted by at least one nitro and/or primary amino group; also, these compounds with further ring substitution with halogeno, methyl, or methoxy groups; (3) similar substances (1) and (2); and (4) auramine or magenta. Overall, there were 104 patients with a possible exposure to bladder carcinogens. Relevant occupations included 44 in rubber, 22 in cables, 26 in gasworks, and 12 miscellaneous (dye and paint manufacture, chemical factories, laboratories, and poison manufacture). (5 refs.)

77-1168 **Epidemiological Aspects in Assessing the Carcinogenic Hazards of Pollution.** (Fre.) Flamant, R. (Unite de Recherches Statistiques INSERM U.21, 94800 Villejuif, France) *INSERM Symposia Series* 52: 275-278; 1976.

The classical epidemiological methods are reviewed: (1) mortality and morbidity statistics; (2) geographical studies and comparisons of specific areas, such as rural and urban regions; (3) migrant studies. Descriptive studies can be of considerable value in identifying a potential carcinogen. Analytical epidemiology, which either projects the incidence of cancer or measures the incidence retrospectively on a chronological basis, can lead with a fair degree of certainty to identification of the responsible factor or factors and help identify the population at risk. (3 refs.)

77-1169 **Dependence of Esophageal Cancer Incidence in the Gurev Oblast on the Mineral Content of Drinking-Water.** (Rus.) Nemenko, B. A. (Kazakh Scientific Res. Inst. Oncology and Radiology, USSR) Moldakulova, M. A.; Zorina, S. N. *Vopr Onkol* 22(9): 75-76; 1976.

The high incidence (no numbers given) of esophageal cancer in the Gurev District (USSR) appears to be related to low levels of molybdenum in the environment and to the salinization of the soil and water with sulfates and chlorides. Molybdenum content in the river water (0.0008-0.0050 mg/liter) and in the soil (0.00009-0.0002%) was significantly lower than the av concentration of this element (0.2 mg/liter and 0.0003%, respectively). (14 refs.)

77-1170 **Neoplastic and Possibly Related Skin Lesions in Neotenic Tiger Salamanders from a Sewage Lagoon.** (Eng.) Rose, F. L. (Biological Sciences, Texas Tech Univ., Lubbock, TX 79409) Harshbarger, J. C. *Science* 196(4287): 315-317; 1977.

Neotenic tiger salamanders, *Ambystoma tigrinum*, were the only vertebrate inhabitants of a small isolated lagoon polluted with sewage. On an annual basis, 30% to 50% of these salamanders developed skin lesions, 84% of which were neoplasms. The neoplastic lesions arose from skin epithelium, dermal fibroblasts, or dermal melanocytes. Tiger salamanders from uncontaminated lagoons in the same area metamorphosed normally and did not develop neoplasms. Chemical analysis of the polluted lagoon revealed 300 ppm of perylene and a trace of benzpyrene. Perylene in combination with other polycyclic aromatic hydrocarbons has been shown to be carcinogenic in mice and rats. Analysis failed to detect volatile amines. Another factor in tumorigenesis is the failure

of the salamanders to metamorphose. This allows the 14- to 17-mo exposure time needed for larval skin to develop neoplasms. Tiger salamanders appear to be sensitive indicators for certain types of environmental carcinogens. (8 refs.)

77-1171 **Some Aspects of the Genetics of Bovine Leukemia Communication. I. Incidence, Age of Onset, Effect of Population Size, Purebloodedness, and Milk Productivity on the Incidence of Leukemia.** (Eng.) Petukhov, V. L. (Dept. Genetics and Breeding Domestic Animals, Novosibirsk Agricultural Inst., USSR) *Sov Genet (Transl)* 11(12):1508-1513; 1976.

The incidence of leukemia, the age of onset, and the effects of population size, purebloodedness, and the level of milk productivity on the incidence of leukemia in dairy herds were studied over a 10-yr period. A population-statistical method was used to study the bovine leukemia morbidity among the Brown Latvian breed in Latvia and the Holstein breed in Novosibirsk. The age of onset of leukemia was calculated from the data for the last 4 yr (1,516 animals). The correlation between leukemia morbidity and level of milk productivity was established using data over a period of 8 yr on 562 leukemic and 1,552 healthy cows. The av age of onset of leukemia among cows was 6.5 yr (4.2 lactations) and among sires was 5.1 yr. The probability of the disease was low in young animals (3-4 yr) and increased in the adult cows; there was no decrease with age. A correlation was found between the age of onset of leukemia in dams and daughters. Significant differences were found between some sires that were used simultaneously in the same farm with respect to age of onset of disease in their offspring. No correlation was found between the incidence of leukemia and population size nor between the degree of purebloodedness and level of leukemia morbidity. Healthy and diseased animals did not differ with respect to milk fat content. Highly productive cows were afflicted with the disease to the greatest extent. The high incidence of the disease among the highly productive cows is apparently related to their intense metabolism and the inadequately balanced nature of the rations, which cause disturbances in the metabolism of some substances and weakening of the resistance of the organism. (17 refs.)

77-1172 **Characterisation of Normal and Pathological Growth of Human Bone Marrow Cells by Means of a New System Cell Assay.** (Eng.) Walther, F. (Universitätsklinik Frankfurt/Main, Abteilung für Hämatologie, 6000 Frankfurt/Main, W. Germany) Schubert, J. C.; Schopow, K. *Haematol Bluttransfus* 19: 47-50; 1976.

The use of cell electrophoresis in combination with a diffusion chamber assay for the characterization of normal and

leukemic human stem cell compartments is described. An electrophoretic cell separator is used for the isolation of human bone marrow cells. After separation, single fractions are tested by a conventional diffusion chamber method for growth and differentiation. NMRI mice are used as the hosts. In order to stimulate erythropoiesis, the animals are kept at 0.5 atmospheres pressure immediately after chamber implantation. Each chamber is filled with 750,000 nucleated cells, and harvesting is done on day 9. When the number of nucleated cells grown in the diffusion chamber is plotted against electrophoretic migration, two different stem cell populations with comparable growth capacity are observed for normal human bone marrow. The bimodal distribution is characterized by maxima at fractions -3 and -6 along the migration coordinate. Application of the method to human acute leukemic cells reveals that only those cells which originate from the region of slow electrophoretic migration (fraction -5 to -10) cause progeny in the diffusion chamber, with only one max observed at fraction -6 along the electrophoretic migration coordinate. The lack of cell growth in the fast migrating

region which contained originally the myeloblasts of the bone marrow may be due to different growth kinetics or insufficient proliferation capacity. The technique may be useful in studying the pathogenesis of human leukemia on the stem cell level. (18 refs.)

See also

- * (Rev.): 77-0603, 77-0604, 77-0631, 77-0635, 77-0636, 77-0637, 77-0638, 77-0639, 77-0640, 77-0641, 77-0642, 77-0651, 77-0662, 77-0679, 77-0680, 77-0683, 77-0700, 77-0712, 77-0717, 77-0720, 77-0721, 77-0722, 77-0723, 77-0730, 77-0743, 77-0745, 77-0754, 77-0755, 77-0756, 77-0757, 77-0759, 77-0760, 77-0761, 77-0762, 77-0763
- * (Chem.): 77-0801, 77-0804, 77-0805.
- * (Viral): 77-0931, 77-0987.
- * (Immun.): 77-1011.
- * (Path.): 77-1052, 77-1098, 77-1108, 77-1117.

MISCELLANEOUS

- 77-1173 **Animal Model of Human Disease: Metastatic Adenocarcinoma of the Prostate.** (Eng.) Polard, M. (Lobund Lab., Univ. Notre Dame, Notre Dame, IN 46556) *Am J Pathol* 86(1): 277-280; 1977.

The characteristics of a transplantable adenocarcinoma of the rat prostate gland that make it a suitable model of metastatic adenocarcinoma of the human prostate are discussed. Three unique transplantable tumor lines were derived from three aged germ-free Lobund Wistar rats in which spontaneous prostate adenocarcinomas were detected. The tumors had spread to other visceral organs, including the lungs. Inoculation of the rat tumor cells into weanling rats produced a small sc nodule at the inoculation site within 10 days. As the tumors enlarged, the central portions were usually degenerated, but cells in the peripheral portions appeared intact. Small foci of tumor cells appeared in the regional lymph nodes and in all successive lymph nodes leading to the thoracic duct and the lungs. Within 3 wk after inoculation, small solid tumor lesions appeared on and in the lungs. By the fourth wk the rats appeared sick. As few as 10 in vitro-propagated tumor cells have induced local plus metastatic tumors in the Wistar rats. Surgical excision of the sc tumor on the 10th day after implantation did not prevent development of lung lesions. The metastatic pattern of tumor cells also followed lymph channels from the hind footpad to ipsilateral popliteal, inguinal, lumbar, and renal lymph nodes to the lungs. Some late lesions have been seen in kidneys and bones. Prostate adenocarcinoma in man spreads via lymphatic routes to lymph nodes, bones, and other organs. In this respect, therefore, the rat prostate tumor system simulates the prostate tumors of man. Thus far, the tumor and its metastatic foci have been inhibited by cyclophosphamide and by *Corynebacterium parvum* and accelerated by whole-body x-irradiation. (6 refs.)

- 77-1174 **A Technique for Developing Established Cell Lines from Human Osteosarcomas.** (Eng.) Veichselbaum, R. (Joint Center Radiation Therapy, Boston, MA 02115) Epstein, J.; Little, J. B. *In Vitro* 12(12): 833-836; 1976.

A method for the development of two human osteogenic sarcomas in established culture is presented. TX-4 was derived from a tumor of the proximal tibia in a 13-yr-old girl; TX-10 was obtained from the scapula of a 10-yr-old boy. The cells were placed in a scored petri dish and covered with a medium of 42.5% Ham's F-10, 42.5% Eagle's Minimal Essential Medium, 7.5% fetal bovine serum, 7.5% horse serum and

supplemented with amino acids, glucose, sodium pyruvate, and Aureomycin. Cells that appeared malignant were grown to confluence and trypsinized into a single cell suspension for cloning. Within 5 days of explantation, the tumor tissue showed outgrowths of fibroblasts; epithelial cells gradually appeared, and these were selected for the cloning. Although once a cloned colony was returned to a monolayer, a period of irregular growth occurred over a period of 2 to 3 mo, stability was eventually maintained. These cultures could then be transferred at 8:1 split ratios without causing significant changes in their growth patterns. The av doubling times for both lines after 100 in vitro passages ranged from 38 to 56 hr with an av of approx 55 hr. Chromosome counts from TX-4 cells indicated numbers ranging from 49 to 59; this was in agreement with previous reports for cultured human osteogenic sarcoma cells. (8 refs.)

- 77-1175 **Human Breast Cancer in Culture.** (Eng.) Trempe, G. L. (Institut d'hematologie-oncologie de Montreal, Quebec, H4J 1C5/Canada) *Recent Results Cancer Res* 57: 33-41; 1976.

Techniques to establish permanent cell lines from human breast cancers and pleural effusions are detailed. Primary cultures were initiated from metastatic pleural fluid obtained from 37 breast cancer patients. Successful primary epithelial outgrowths were obtained for 24/31 of the scirrhous-type tumor cells and for 6/6 of the other histological types. From these primary cultures, two permanent cell lines (> 50 passages) were established. One of these, SK-BR-3, was obtained from blood-filled pleural fluid of a patient found at autopsy to have a metastatic adenocarcinoma of the left breast. A glass-attached cell population rather than a suspension culture was deliberately selected. The second line, SK-OV-1, was obtained from a clear pleural effusion of a patient who had a highly anaplastic breast tumor at autopsy. Chromosome studies on both cell types showed that the model range of SK-BR-3 cells were hypertriploid to hypotetraploid with chromosomes showing large, submetacentric markers. Cells of SK-OV-1 were hypodiploid to hypertetraploid with double ring markers on chromosomes. Neither viruslike particles nor estrogen-binding receptors were demonstrated in either cell line. (13 refs.)

- 77-1176 **Establishment of a Continuously Growing Cell Line from Primary Carcinoma of the Liver.** (Eng.) Alexander, J. J. (Virus Cancer Res. Unit, Johannes-

burg, South Africa) Bey, E. M.; Geddes, E. W.; Lecatsas, G. *S Afr Med J* 50(54): 2124-2128; 1976.

The establishment of a continuously growing cell line from primary carcinoma of the liver is discussed. The cell line was initiated from the multifocal areas of outgrowth in the primary culture. The tumor cells were considered adapted to in vitro conditions after 1 yr (8th to 9th passage) but were regarded as a cell line only after 18 mo in culture, when it became possible to store the cells at -70 C in a freezing mixture containing 40% fetal bovine serum, 50% minimum essential medium with nonessential amino acids, and 10% glycerol and to reinitiate growth after thawing. At present (40th passage), the cultures can be passaged at 1:6 dilution, the plating efficiency is 40-50%, and the cell doubling time is 35-40 hr. The cells are polygonal in shape with well-defined borders. Confluent cultures or confluent areas within cultures have a greater proportion of smaller cells compared with the edges of growing islands, and in these cells the cytoplasm is more granular. Many of the cells are binucleate, a property of hepatocytes in culture. The growth pattern is typical for epithelial cells: islands of outgrowth occur as the cells multiply in sparse culture, and trypsinization produces large clusters of tightly packed cells. Trypsin plus versene is required for monodisperse suspensions. The karyology of the cells is male and human. The numerical chromosome analysis of 100 complete and well-spread metaphase plates of the hepatoma cells demonstrated a distribution of 48-61 with an av number of 56. The enzymes conformed to the human pattern, and the cells contained the type A glucose-6-phosphate dehydrogenase. Extremely low levels (3-4 nanograms/ml) of α -fetoprotein were detected. Ultrastructurally, the cells had a dense cytoplasmic matrix with few elements of the endoplasmic reticulum, abundant polysomes, and mitochondria with a dense matrix. Lysosomelike structures containing membrane fragments and other electron-dense material were common. The nuclei were characterized by the absence of condensed chromatin, either marginal or in clumps dispersed in the nucleoplasm. Most cells had more than one nucleolus that invariably consisted of the nucleolonema only. Virus particles were not detected by electron microscopy. The cell line is derived from male, human, malignant liver tissue. (24 refs.)

77-1177 Human Pancreatic Carcinoma (MIA PaCa-2) in Continuous Culture: Sensitivity to Asparaginase. (Eng.) Yunis, A. A. (Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL) Arimura, G. K.; Russin, D. J. *Int J Cancer* 19(1): 128-135; 1977.

The establishment and partial characterization of a cell line from an undifferentiated pancreatic carcinoma are described. Tumor tissue was excised preoperatively from a mass involving the pancreatic body and tail in a 65-yr-old man. Cell cultures were prepared with Dulbecco's modified Eagle's

medium with 10% fetal calf serum and 2.5% horse serum, with eventual elimination of all fibroblasts. The epithelial cell line established, MIA PaCa-2, which has undergone 100 transfers, has a doubling time of 40 hr. The cells are large with abundant cytoplasm, two to four nucleoli, high aneuploidy (chromosome numbers of 58-71), and an agar colonization efficiency of 19%. The cells were positive for Sudan Black B stain, fat droplets, and isoenzyme B of glucose 6-phosphate dehydrogenase and negative for trypsin, chymotrypsin, carcinoembryonic antigen, alkaline phosphatase, and viral particles. Growth inhibition was greatest with vincristine and L-asparaginase, but the former response was non-specific. L-asparaginase suppression was specific, with 0.1 international unit (IU)/ml inducing significant inhibition and 0.5-1.0 IU/ml causing complete inhibition and cell death. (15 refs.)

77-1178 The Phenotypic Abnormality in Leukemia: a Defective Cell-Factor Interaction? (Eng.) Wu, A. M. (Dept. Molecular Biology Bionetics Res. Lab., NCI, NIH, Bethesda, MD 20014) *Haematol Bluttransfus* 19: 51-62; 1976.

Experimental approaches designed to investigate the relationship between cell-factor interaction and leukemogenesis are discussed. The interaction of myelogenous cells with factor(s) leading to differentiation can be measured either with a suspension mass culture method or by a solid (semi-soft) clonal method. The protein factors that support the growth of hemopoietic cells are termed growth stimulating activity (GSA) for suspension culture and colony stimulating activity (CSA) for semi solid culture. Preliminary studies using conditioned medium prepared from phytohemagglutinin stimulated human lymphocytes (PHA-LyCM) and whole human embryo cells revealed that GSA and CSA are not identical for the growth of normal or leukemic WBC. Fractionation of PHA-LyCM showed that there are three peaks for CSA. Each peak contains different fractions for supporting cell proliferation, differentiation, and the self-renewal of precursor cells in suspension culture. Apparently, each contains heterogeneous species of protein factors, some of which functionally overlap. Although the results are preliminary, it appears feasible to study a specific interaction between protein factor and their specific target cells with fractionated defined factors. The clarification of cell-factor interactions should prove useful for distinguishing between the accumulation of normal immature cells and of abnormal blood cells. (34 refs.)

77-1179 Cellular Subclasses in Human Leukemic Hemopoiesis. (Eng.) Till, J. E. (Ontario Cancer Inst. and Sunnybrook Medical Centre, Univ. Toronto, Toronto, Canada) Mak, T. W.; Price, G. B.; Senn, J. S.; McCulloch, E. A. *Haematol Bluttransfus* 19: 33-45; 1976.

vidence that some of the organizational and regulatory features of normal hemopoiesis persist in human leukemia is presented. Results using cell cultures provide some support for the view that leukemic hemopoiesis, like normal hemopoiesis, involves three levels of differentiation: leukemic stem cells, committed leukemic progenitors, and more mature cells. Leukemic populations may be organized into cell lines and regulated by messages from the environment in a manner analogous to normal hemopoiesis. On this assumption, it should be possible to identify a class of "managerial cells" in leukemia. At present it is not known whether the messages originate from cells within the leukemic population or from normal managerial cells or both. The apparent similarities between leukemic and normal hemopoiesis raise the possibility that the target cell for leukemic transformation is the normal pluripotent stem cell. If this view is correct, then the various types of leukemia must be determined by the transforming events rather than by the cell class in which they occur. The development of culture methods for the production of leukoviruslike particles from human leukemic cells provides a possible first step toward the direct identification of leukemic target cells. (47 refs.)

77-1180 **The Fine Structure of Three-Dimensional Colonies of Human Glioma Cells in Agarose Culture.** (Eng.) Carlsson, J. (Dept. Physical Biology, Gustaf Werner Institute, Univ. Uppsala, Uppsala, Sweden) Brunk, U. *Acta Pathol Microbiol Scand (A)* 85(2): 183-192; 1977.

The fine structure of human glioma cells (118 MG) cultivated as three-dimensional spherical colonies in agarose was investigated during exponential growth. All the variables were measured as a function of depth in the colonies. The colonies did not show central degeneration even though they reached diameters of up to 600 μm . The mitotic index decreased almost exponentially with the distance from the surface, indicating that a proliferative gradient existed in the colonies. The radial distance at which the mitotic index changed by a factor of 2 was 90 μm (nearly 5 cell diameters). Large extracellular spaces extended throughout the colonies, the mean volume of which increased from 20% in the periphery to 40% in the central region. The mean volumetric fractions of cytoplasm and nuclei and the quotient between nuclei and cytoplasm decreased slightly with depth in the colonies. Cytoplasmic extensions, with a rufflinglike appearance, occurred both at the periphery and in the center of the colonies, but were larger and more frequent at the periphery. The fractions of mitochondria and vacuoles in the cytoplasm showed large local variations. The mean number of mitochondria decreased somewhat toward the center and the number of vacuoles containing a highly electron-absorbing substance increased in the most central regions. These studies indicate that it is possible to investigate the growth pattern of tumor cells, cultivated as three-dimensional spheroids, in detail and at the amount of cytoplasm, nuclei, extracellular space, cellular structures, and proliferation can be quantified as a function of the distance from the surface. (16 refs.)

77-1181 **Colon Carcinoma: Its Genesis and Chalone Control.** (Eng.) Kanagalingam, K. In: *Chalones*. Houck, J. C., ed. (New York: American Elsevier Publishing Co., Inc.): pp. 459-482; 1976.

Evidence that extracts of human colon carcinoma cells (SW-48) and also of normal colonic cells contain an inhibitor of mitosis is reviewed. This inhibitory fraction acts in G_1 , is not species specific or cytotoxic, and has a reversible effect which is organ specific. Thus the inhibitor has the characteristics of a chalone. The proliferation of SW-48 cells was followed in vitro by cell counting and study of thymidine uptake. The inhibitory fraction is in the molecular wt range of 10,000-50,000 daltons. (112 refs.)

77-1182 **Molecular Mechanisms in Erythroid Differentiation.** (Eng.) Paul, J. (Beatson Inst. Cancer Res., 132 Hill St., Glasgow G3 6UD, Scotland) *Haematol Bluttransfus* 19: 125-135; 1976.

Molecular mechanisms involved in erythroid differentiation are examined, with particular emphasis on the control of globin synthesis. When Friend cells are grown in suspension cultures, they have a doubling time of 12-14 hr and rarely show evidence of hemoglobinization. Following treatment with 2% dimethylsulfoxide (DMSO), Hb synthesis occurs at a high rate after a lag period of 24-48 hr. The cells rapidly become hemoglobinized until, after about 5 days, upwards of 80% of the cells contain large amounts of Hb. Simultaneously, these cells exhibit other phenomena characteristic of erythroid differentiation. Cell division diminishes and eventually ceases irreversibly. RNA synthesis also diminishes, and the nucleus becomes condensed. The accumulation of Hb is accompanied by an accumulation of globin messenger RNA (mRNA). In normal differentiation, it is likely that erythropoietin is responsible for an early event which results in the commitment of erythropoietin sensitive cells to erythroid differentiation. Experiments with cultured mouse fetal liver suggest that the continued presence of erythropoietin accelerates the completion of maturation. In the course of normal erythropoiesis, it may be assumed that there is an adequate production of heme; but this may be rate-limiting in many Friend cells, and the DMSO effect may be related to increasing heme availability. The regulation of maturation of erythroid cells involves a series of coordinated events which include, among others, the following: the rate of transcription of the globin gene which appears to increase on the induction of many inducible Friend cells; the rate of translation for which there is evidence in all varieties of the Friend cell studied. This may be an important mechanism in vivo as suggested by the fact that globin mRNA can be detected in large amounts in basophilic erythroblasts before Hb synthesis is detectable. (30 refs.)

- 77-1183 **Erythroid Cell Differentiation.** (Eng.) Forget, B. G. (Div. Haematology-Oncology, Dept. Medicine, Children's Hosp. Medical Center, Sidney Farber Cancer Center, Harvard Medical Sch., Boston, MA 02115) Glass, J.; Housman, D. *Haematol Bluttransfus* 19: 109-124; 1976.

Erythroid cell differentiation is discussed in terms of alterations which can occur in the normal pattern of erythroid cell development during the course of leukemia. Quantitation of heme and globin synthesis and globin messenger RNA (mRNA) during murine erythroid cell maturation is also discussed. During the course of many leukemias, there is a synthesis of red cells containing fetal Hb (Hb F) usually involving small populations or clones of red cells and probably representing a nonspecific response of the bone marrow to hematologic stress. However, in juvenile chronic myeloid leukemia (CML) and in rare cases of erythroleukemia, there is a major reversion to fetal erythropoiesis. This involves a progressive increase in Hb F levels and the synthesis of red cells which have a true fetal pattern of protein synthesis affecting the Hb adult (A)₂, carbonic anhydrase, and the membrane antigens i (fetal) and I (adult). In juvenile CML, the fetal erythropoiesis may be a more specific manifestation of the leukemic process, related to the phenomenon of fetal protein synthesis (α -fetoprotein of carcinoembryonic antigen) observed in other types of neoplasia. Measurement of globin mRNA levels in separated populations of murine erythroid cells at different stages of maturation have demonstrated a correlation with the degree of morphological maturation. In the least well differentiated cells, there appears to be a disproportionate amount of mRNA for the level of Hb synthesis. Thus, the presence of some translational control of globin mRNA in the early stages of erythroid development is suggested, although the major control of globin gene expression in this system seems to be at the transcriptional level. When the immature erythroid cells are cultured in the presence of erythropoietin, de novo synthesis of ³H-uridine labeled globin mRNA can be demonstrated by the specific RNA-complementary DNA hybridization assay. (27 refs.)

- 77-1184 **Increase in Globin Chains and Globin mRNA in Erythroleukemia Cells in Response to Hemin.** (Eng.) Dabney, B. J. (Dept. Pediatrics, Baylor Coll. Medicine, Houston, TX 77030) *Arch Biochem Biophys* 179(1): 106-112; 1977.

The effects of hemin on clone 745 of Friend erythroleukemia cells (GM-86) were investigated. The addition of 50 μ M hemin to a culture medium containing 0.5% dimethyl sulfoxide (DMSO) resulted in a significant increase in globin chain synthesis, as measured by a 1-hr incorporation of radioactive leucine after 5 days of growth. Increased globin chain synthesis with addition of hemin was also noted with 0.1%-1.5% DMSO. ⁵⁹Fe-heme synthesis was also greatly stimulated by

induction of erythrodifferentiation with 1.5% DMSO. The addition of 15 mM 3-amino-1,2,4-triazole (AT) to 1.5% DMSO-induced cultures reduced ⁵⁹Fe-heme and globin chain synthesis to uninduced levels. Cultures containing 25 μ M hemin in addition to 15 mM AT and 1.5% DMSO were protected from the inhibition of globin synthesis by AT. The addition of AT resulted in approx a 50% reduction of cell number, but it did not affect cell viability, as measured by trypan blue exclusion. Addition of hemin did not protect against the reduction in cell number. The percentage of benadryl-positive cells after 5 days of growth was 54% for 1.5% DMSO, < 5% for 1.5% DMSO plus AT, and 79% when 25 μ M hemin was added with the DMSO and AT. There was a significant increased globin messenger RNA (m)RNA content with induction by 1.5% DMSO and an intermediate level with 0.5% DMSO. The addition of 50 μ M hemin to cultures containing 0.5% DMSO increased mRNA content to approx the fully induced level. Results of globin chain analysis indicated a greater than tenfold stimulation when 50 μ M hemin was added to cultures containing 0.5% DMSO. Globin synthesis in 1.5% DMSO-induced cultures was reduced approx fivefold by the addition of AT. The mRNA content of cultures grown in 1.5% DMSO was greatly increased compared to control cultures. The addition of 0.5% DMSO resulted in a four- to eightfold increase of globin mRNA content. The addition of 50 μ M hemin to cultures of 0.5% DMSO, however, caused an additional fourfold increase of globin mRNA. Exogenous hemin may promote globin chain synthesis, and endogenously synthesized heme may be required for globin chain synthesis, and hemin may alter the appearance or degradation of globin mRNA sequences in the cytoplasm. (10 refs.)

- 77-1185 **Amino Acid Concentrating Ability of Slow Growing Autochthonous Hepatomas and Host Livers.** (Eng.) Kelley, D. S. (McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI 53706) Potter, V. R. *Biochem Biophys Res Commun* 75(2): 219-225; 1977.

To determine if an increase in the intracellular concentration of amino acids always accompanies the development of a neoplasm, slowly growing autochthonous hepatomas were developed in 43 Buffalo rats. The animals were fed a 30% casein diet containing 0.02% 2-acetylaminofluorene for 30 days and then 0.05% phenobarbital (PB). Single injections of 100 mg/kg of nitrosodimethylamine (DMN, 5.5 or 11.0 mg/kg body weight) were given to the animals 23 or 30 days before the end of the experiment. Survivors were killed after 259, 288 or 295 days on PB-containing diet. It was found that the resulting 1-hepatomas concentrated less than one half the amount of nonmetabolizable α -aminoisobutyric acid (AIB) than did the respective host and control livers when AIB was injected 1 hr before sacrifice. The ability to concentrate AIB was fourfold among hepatomas within a single liver as well as among hepatomas from different animals. While an increase in the ability to concentrate amino acids may be necessary for rapid

growth, it was not a concomitant of neoplastic transformation. The narrow range of AIB concentrations found among the 123 slowly growing autochthonous hepatomas compared with the wide spectrum of AIB concentrations already encountered in several transplantable Morris hepatoma lines, suggests that these tumors were at one of the earliest stages of their progression. (29 refs.)

77-1186 The Functional Significance of Oncocytes (the "B" Cells). (Eng.) Raikhlin, N. T. (Lab. Histochemistry and Electron Microscopy, Dept. Pathological Anatomy of Human Tumors, Inst. Experimental and Clinical Oncology, Acad. Medical Sciences USSR, SSSR 115478 Moscow, Kashirskoye Chaussee 6, USSR) *Acta Histochem (Jena)* 57(1): 49-54; 1976.

The possible function of oncocytes in relation to the accumulation of serotonin was investigated. The study material consisted of 38 salivary gland tumors, 25 lung tumors, 12 laryngeal tumors, and 5 esophageal tumors obtained during operation. In each case, tissue specimens from sections of the organ that were histologically normal were examined. In all organs studied, oncocytes had the same histological structure: large cells with eosinophilic granular protoplasm, usually with a round nucleus. The oncocytes had a very high succinate dehydrogenase activity and contained several biogenic monoamines, including serotonin. The results indicate that oncocytes, irrespective of their localization in a particular organ, possess an active function that is dependent on the presence of serotonin. Oncocytes are not, therefore, a functional dying cells, but rather have an active role in the control of physiological and pathological conditions, in the functioning of a particular organ, and in the homeostasis of the body as a whole. Considering the neuroendocrine action of serotonin and these findings on oncocytes, it is possible to envisage the existence in the human body of an unknown group of serotoninocytes in the guise of a diffuse peripheral neuroendocrine system, widely represented in many organs and tissues. (23 refs.)

77-1187 Reassociation of Rat Hepatoma Chromatin Protein Components with DNA. (Eng.) Tohno, Y. (Lab. Cell Biology, Dept. Anatomy, Nara Medical Univ., Kashihara, Nara 634, Japan) Tohno, S.; Takakusu, A. *Cell Struct Funct* 1(4): 355-365; 1977.

ascites hepatoma chromatin, composed in mass ratios of DNA 1.00, histones 1.08, chromatin nonhistone (CNH) proteins 0.85, was dissociated in 2 M NaCl-5 M urea-50 mM sodium acetate (pH 6.0) and reconstituted by gradient dialysis against decreasing concentrations of NaCl in the presence of urea. The mode of reassociation of chromatin protein components with DNA was examined by gel electrophoresis.

Histone 1 was the first component to bind to DNA, at 0.4-0.2 M NaCl in the presence of urea; the other histone fractions started to reassociate at 0.3 M NaCl and were completely reassociated at 0.1 M NaCl. About one-half of the dissociated CNH proteins reassociated with DNA before all the histones completed their binding to DNA, and about one-half reassociated after that. However, the amount of CNH proteins that reassociated with DNA before the binding of histone 1 to DNA remains to be determined. (33 refs.)

77-1188 Surface Exposure of Glycosaminoglycans in Resting, Growing and Virus Transformed 3T3 Cells. (Eng.) Vannucchi, S. (Inst. General Pathology, Univ. Florence, 50134 Florence, Italy) Chiarugi, V. P. *J Cell Physiol* 90(3): 503-509; 1977.

Glycosaminoglycans (GAGs) were released by trypsin from the surface of 3T3 cultured Swiss mouse cells at two stages of growth: during log-growth phase and during the resting phase. Cells were labeled with ^3H -glucosamine and ^{35}S -sulfate. Doubly labeled molecules from resting cells were compared with those from growing cells as well as cells transformed by polyoma or SV-40 viruses. Reproducible differences in the elution pattern during ion-exchange chromatography and in susceptibility to specific hydrolytic enzymes were noted. The GAGs pattern of growing normal cells was similar to that of the transformed cells but very different from the pattern of resting cells. Growing and transformed 3T3 cells showed a relatively large amount of hyaluronic acid (HA); this ratio was reversed in resting cells. The lowering of HS and the increase of HA in the cell coat is therefore believed to be more dependent upon growth than upon transformation. (15 refs.)

77-1189 Surface Properties of Normal and Neoplastic Rat Liver Cells. Lectin-Induced Cytoagglutination and Lectin Receptor Activity of Cell-Surface Glycopeptides. (Eng.) Starling, J. J. (Biochemisches Institut der Universität Freiburg im Breisgau, Hermann-Herder-Strasse 7, D78 Freiburg im Breisgau, W. Germany) Capetillo, S. C.; Neri, G.; Walborg, E. F. *Exp Cell Res* 104(1): 177-190; 1977.

The surface properties of neoplastic and normal rat liver cells are assessed. Rat liver cells were isolated by enzymatic dissociation by perfusion with collagenase and, in addition, by perfusion with citrate followed by mechanical dispersal. The lectin-induced agglutination was quantitated using two complementary assays that measured the degree of agglutination as a function of the size of the cell aggregates (Microtest II plates) or the disappearance of single cells (electronic particle counter). Hepatocytes prepared by mechanical dispersal were not agglutinated by high concentrations of wheat germ agglutinin (WGA) or concanavalin A (Con A). Enzymatically

(collagenase) dispersed hepatocytes were agglutinated by low concentrations of Con A or WGA. Papain treatment significantly altered the lectin-induced agglutinability of enzymatically dispersed hepatocytes. Papain treatment was accompanied by a four- or eightfold reduction in the lectin concentration required for threshold agglutination by Con A or WGA, respectively. Comparison of the gel filtration profiles of the glycopeptides released from the surface of hepatocytes and Novikoff hepatoma cells suggested major qualitative differences in their plasma membrane glycoproteins. In contrast to the cell-surface sialoglycopeptides from hepatocytes, a major portion of the sialoglycopeptides from Novikoff cells was excluded from the gel. This fraction contained 31% of the total sialic acid released from the cell surface by papain. The glycopeptides isolated from the surface of enzymatically dispersed hepatocytes possessed no detectable Con A or WGA receptor activity, indicating that the cell surface components responsible for the agglutination of rat hepatocytes are not released by digestion with papain. On the other hand, the cell-surface glycopeptide fractions from Novikoff cells possessed potent Con A and/or WGA receptor activity. (39 refs.)

- 77-1190 Mouse Pituitary Tumor mRNA Directed Cell-Free Synthesis of Polypeptides That are Cross-Reactive with Adenocorticotrophic Hormone Antiserum.** (Eng.) Jones, R. E. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032) Pulkrabek, P.; Grunberger, D. *Biochem Biophys Res Commun* 74(4): 1490-1495; 1977.

The mouse pituitary tumor AtT-20 messenger RNA (mRNA)-directed cell-free synthesis of polypeptides was evaluated. A wheat germ extract was used to translate the mRNA isolated from AtT-20. All reactions that contained AtT-20 RNA resulted in the synthesis of polypeptides that were precipitated by a double-antibody technique directed against ACTH polypeptide $\beta(1-24)$. The highest stimulatory activity was achieved by the 14S-22S RNA fraction. The specificity of the immunoprecipitation was proved by using globin mRNA instead of AtT-20 mRNA, adding cold $\beta(1-24)$ to the immunoprecipitation reaction mixture, or by using nonimmune rabbit serum instead of anti- $\beta(1-24)$ serum. There was no significant formation of radioactive immunoprecipitates in all these cases. The cell-free synthesized products directed by AtT-20 total RNA were analyzed by radioimmunoassay. The products were subjected to Sephadex G-50 column chromatography, and each fraction was assayed for immunoreactive ACTH polypeptides using porcine ^{125}I - $\alpha(1-39)$ ACTH as the tracer. Immunoreactive ACTH-like peptides migrated in and near the void volume, indicating a molecular wt of $> 20,000$. The products of the reaction mixtures were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis. A heterogeneous profile of the newly synthesized proteins was noted when 14S-22S AtT-20 poly(A)-containing RNA was utilized. When the

polypeptide products from this reaction were subjected to a double-antibody immunoprecipitation technique using affinity purified $\beta(1-14)$ antiserum, the radioactive material in the washed immunoprecipitate migrated as a well-defined peak. The estimated molecular wt of the immunoreactive ACTH protein was determined to be 31,000, since it comigrated with deoxyribonuclease I. The faster moving components in the immunoprecipitate were probably nascent, incomplete ACTH polypeptides that were also detected on the Sephadex G-50 chromatogram. When the 0-135 AtT-20 poly(A) RNA fraction was used in the cell-free protein-synthesizing reactions, the immunoprecipitated material contained only the 31,000-molecular-wt species, which may be the initial gene product. (11 refs.)

- 77-1191 Ultrastructure and Cytochemistry of Ehrlich Ascites Cells of the Strain HD 33: Masked Protein in Glycogen Deposits.** (Eng.) Zimmerman, H. P. (Institut für Zellforschung, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany) Granzow, V.; Granzow, C. *J Ultrastruct Res* 57(2): 140-149; 1976.

The recently established HD 33 Ehrlich ascites tumor cells (derived from G+ cell line which originates from glycogen-storing cells) grown in vivo of the incidence of leukemia vs T65D data, significant changes are noted. obtained from the peritoneal cavities of male NMRI mice (20-25 g) which had been injected ip with 10^7 washed tumor cells 84 hr or 7-8 days before; cells were subcultured daily for in vitro study. Cells showed faint to very intense color reaction when stained with toluidine blue; this individual variation is uncommon to Ehrlich ascites cells. HD 33 cells showed extensive invagination of the nuclear envelope as a whole or of its inner membrane. During exponential growth phases in vivo and in vitro, glycogen deposits were found predominantly in the cytoplasm; it was deposited mainly intranuclearly under normal growing conditions in vitro as well as in the course of growth retardation in vivo. β -glycogen particles were observed in vivo and in vitro, whereas α -glycogen particles were restricted to in vivo conditions. Treatment with amyloglucosidase led to disappearance of glycogen particles and the formation of a Pronase-sensitive reticular network, the role of which is being investigated. (25 refs.)

- 77-1192 Unique Melanosomal Proteins in Murine Melanoma.** (Eng.) Klingler, W. G. (Dermatology Branch, NCI, NIH, Bethesda, MD) Montague, P. M.; Hearing, V. J. *Pigm Cell* 2: 1-12; 1976.

Melanin granules, purified from normal and malignant murine melanocytes, were solubilized with Triton X-100 and fractionated by polyacrylamide gel electrophoresis. The fol-

Following classes of proteins were observed: (1) those common to all tissues; (2) those found in normal melanosomes but absent in melanoma; and (3) those unique to murine melanoma. The unique melanosomal proteins have several possible origins: (1) fetal proteins derepressed in the malignant cells; (2) viral origin; and (3) a result of malsynthesis or aberrant degradation. There is some evidence that melanin granules may be of significance in the immune response to melanoma, but the unique melanoma melanosomal proteins have yet to be shown to be immunogenic *in vivo*. Preliminary results from a search for unique proteins responsible for tumor-specific circulating antibodies in human melanoma indicate a pattern similar to the murine melanosomal proteins. (38 refs.)

77-1193 **Particulate and Soluble Tyrosinases of Human Malignant Melanoma.** (Eng.) Nishioka, K. (Surgical Research Lab., RI 409, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX 77030) Romsdahl, M. M. *Pigm Cell Res* 121-126; 1976.

The nature of the particulate form of trypsinase, obtained from human malignant melanoma by detergents and sonication, and its potential relation to the soluble form of the enzyme are discussed. Particulate tyrosinase yielded a smaller, fast-migrating tyrosinase that appears to correspond to one of the naturally soluble forms of this enzyme. Treatment of the larger particulate enzyme form with trypsin augmented the development of the faster-migrating tyrosinase. Treatment of a human malignant melanoma homogenate with a fine protease inhibitor, phenylmethylsulfonyl fluoride, blocked the release of the smaller tyrosinase. Further study suggested that cathepsins are not responsible for the breakdown of particulate tyrosinase. These findings are compatible with earlier results, which indicated that lipase-solubilized, particulate tyrosinase was similar to the naturally soluble enzyme with respect to activity and gel electrophoresis pattern. These findings support the interpretation of the dynamic transition of the particulate form of tyrosinase to the soluble form. Since soluble tyrosinase is a minor part of the total tyrosinase activity in most mammalian systems, soluble tyrosinase may be a proteolytic product of particulate tyrosinase. (12 refs.)

77-1194 **Localization of Specific Phosphatase Producing Reticular Cells in the In five mice injected with 10⁶ RUF and 10⁴ LUF simultaneously, Parenchyma of Normal and Tumor-Bearing Mice.** (Fre.) Catayee, G. (Laboratoire d'Histologie, Faculte de Medecine, 2 rue Ecole

de Medecine, 34000 Montpellier, France) *C R Soc Biol* 170(4): 794-797; 1976.

In the mouse, four types of spleen reticular cells with different enzymatic activity can be identified by histochemical techniques: (1) endothelial-alkaline phosphatase, (2) endothelial-adenosine triphosphatase (ATPase), (3) perithelial-5' nucleotidase, (4) phagocytic-acid phosphatase. The spleens of normal C3H mice were compared with those of tumor-grafted mice who developed mammary carcinomas. The enzymatic activity of alkaline phosphatase producing cells was markedly in the multiply injected group. In the B-16 mice, palpable tumors appeared in the tumor-bearing mice. The morphology of the white tissue of the grafted mice was altered, with cells secreting alkaline phosphatase forming a thick membrane on the periphery of the lymphoid sheath. Contrary to their distribution in normal rats, where they were concentrated in the red tissue and in the cords of Billroth, the cells secreting acid phosphatase were found throughout the spleen of the tumorous mice. It is postulated that changes in the splenic endothelial cells secreting alkaline phosphatase are evidence of a defense mechanism in mice with malignancies. (7 refs.)

77-1195 **Characteristics of the Enzyme Uridine-Cytidine Kinase Isolated from a Cultured Human Cell Line.** (Eng.) Drake, J. C. (Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD 20014) Stoller, R. G.; Chabner, B. A. *Biochem Pharmacol* 26(1): 64-66; 1977.

The isolation and kinetics of uridine-cytidine kinase (UCKase) from a human lymphoblastic leukemia cell line, CEM, were described. The enzyme is putatively responsible for the phosphorylation of the antileukemic agent 5-azacytidine (AC), and its partial deletion elicits resistance to AC in murine leukemic cells. AC concentrations of 10⁻⁶ M produced 50% inhibition of CEM cell growth *in vitro* at 48 hr, similar to that for L1210 leukemia. Based on a high *K_m* of 11 mM and a *K_i* of 17 mM, AC was found to have a low affinity for UCKase, which was present at levels comparable to those of deoxycytidine kinase. The UCKase from both CEM and acute myelocytic leukemia cells had comparable affinities for AC. UCKase levels are lower than those for cytidine deaminase in leukemic cells, and high AC levels would be required to achieve the *K_m* of UCKase. Because of its lability and rapid metabolism by cytidine deaminase, high AC doses would be therapeutically obligatory; its neurotoxic and gastrointestinal sequelae are known. UCKase levels are also lower than cytidine deaminase in human myeloblasts. The low UCKase levels in leukemic cells relative to cytidine deaminase and the low affinity of UCKase for AC suggest that nucleotide formation from AC and incorporation into RNA are not the sole explanations for its cytotoxicity. Deamination to 5-azauridine or ring cleavage might also be responsible for active metabolite formation. (13 refs.)

- 77-1196 Some Characteristics of Isoenzyme Spectrum of Hexokinase and Glucose Level in Hepatomas and Liver of Host Organism.** (Eng.) Shapot, V. S. (Oncological Res. Center, Acad. Sciences USSR, Moscow, USSR) Gorozhanskaya, E. G.; Lyubimova, N. V. *Biochemistry (Transl)* 41 (part 1, 10): 1433-1438; 1976.

The activity of hexokinase (HK) and its isoenzyme spectrum was studied in hepatoma 22a (a rapidly growing, highly malignant hepatoma), hepatoma 49 (a noninvasive but malignant tumor that behaves like a benign tumor), hepatoma 61 (a slowly growing but decidedly malignant tumor), and in the livers of normal and hepatoma-bearing C3HA mice. The HK activity of hepatoma 22a was four times that of normal liver, the activity of hepatoma 61 was three times higher, and that of hepatoma 49 was two times higher at glucose concentrations of 0.1 and 5.5 mM in the medium. There is evidently a direct correlation between the degree of tumor malignancy, rate of growth, and HK activity. Glucose was almost absent from hepatomas 22a and 61 but was always found in hepatoma 49, where the amount was only slightly lower (1-3.6 mg/g tissue) than that in normal liver (3.3-5.0 mg/g). At a glucose concentration of 0.1 mM, only HK-3, which has the highest affinity for glucose, was active in all the hepatomas studied. In livers of mice with hepatomas, there were changes in the total activity and isoenzyme spectrum of HK, and they tended to be similar to the spectrum in the tumor itself (increase in total HK activity, decrease in glucokinase activity, and increase in HK-3 activity). The dissimilar changes in the total activity and isoenzyme spectrum of HK indicate that these characteristics are secondary and depend on the degree of tumor progression. (17 refs.)

- 77-1197 Cell Recognition and Adhesiveness: A Possible Biological Role for the Sulfated Mucopolysaccharides.** (Eng.) Dietrich, C. P. (Departamento de Bioquímica e Farmacologia Escola Paulista de Medicina C. P. 20372, 01000 Sao Paulo, SP, Brazil) Sampaio, L. O.; Toledo, O. M.; Cassaro, C. M. *Biochem Biophys Res Commun* 75(2): 329-336; 1977.

A possible role for the sulfated mucopolysaccharide (SMPS) in cell recognition and adhesiveness is proposed. Its composition in muscle, ileum, brain and kidney of neonate, adult and tumoral tissue from guinea pigs, rabbits, and humans was determined. Each tissue had a characteristic composition of chondroitin sulfate A/C (ChS A/C), chondroitin sulfate B (ChS B) and heparitin sulfate (HTS). Neonate and solid human tumor tissues (adenocarcinoma, pleomorphic adenoma, leiomyoma and epidermoid carcinoma) contained large amounts of ChS A/C, which was nearly absent in most adult and normal tissues, respectively. Chondroitin sulfate C accounted for 70% of this total chondroitin sulfate. On histologic examination of tumors, ChS A/C was present in the intercellular space. Decrease in HTS was observed in brain

when adult and neonate tissues were compared. No significant changes in its absolute concentration were observed in three out of four tumors when compared with normal adjacent tissues. Results suggest that type and relative proportions of heparitin sulfate and chondroitin sulfate B are the determinants for cell recognition and adhesion. (12 refs.)

- 77-1198 Receptors for Steroid Hormones in Human Melanoma.** (Eng.) Neifeld, J. P. (Surgery Branch, NCI, NIH, Bethesda, MD 20014) Lippman, M. E.; Fisher, R. I. *Surg Forum* 27: 108-110; 1976.

Human melanoma samples were evaluated for steroid hormone receptors. Assays were performed within 2 wk of sample collection. A dextran-coated charcoal assay was used to determine the estrogen, progesterone, and glucocorticoid-binding activity, and a protamine sulfate assay was used to determine androgen-binding activity. A total of 35 patients had tumor samples assayed for steroid hormone receptor activity: the tumor was from the primary lesion (3 patients), a soft-tissue recurrence (13), a metastatic lymph node (17), a liver metastasis (1), and a pulmonary metastasis (1). Sixteen patients were men, and 19 were women. Estrogen receptor activity was present in 16/35 patients. Scatchard analysis of binding in one case was consistent with a single class of receptor sites with a dissociation constant of approx $4.9 \times 10^{-9} M$ and approx 24.7 femtomoles of specific binding per mg of protein. Androgen receptor was observed in 5/30 patients (with 6 equivocal), progesterone receptor in 6/27 patients (with 2 equivocal), and glucocorticoid receptor in 5/26 patients. Estrogen and androgen receptors were found concomitantly in two patients, estrogen and progesterone in four, estrogen and glucocorticoid in three, and estrogen, androgen, and progesterone in one patient. Five patients with no estrogen receptor had specific binding for another class of steroid hormones. The investigation has demonstrated that specific steroid hormone receptors are present in human melanoma. The use of hormone receptor analyses may permit selection of a subset of patients with disseminated melanoma who might be candidates for a trial of hormonal therapy. (5 refs.)

- 77-1199 Thyrotropin Stimulation of ^{32}P Incorporation into the Phospholipids of Canine Thyroid Adenocarcinoma.** (Eng.) Schneider, P. B. (33 Brookline Ave., Boston, MA 02215) Leav, I. *Endocrinology* 100(2): 346-350; 1977.

Thyrotropin stimulation of ^{32}P incorporation into the phospholipids of six carcinomas of the canine thyroid was studied. The first case was diagnosed as hyperthyroid from clinical evidence (wt loss, tachycardia, polyuria) and the finding by ^{131}I scan of a suppressed thyroid lobe. The second case was diagnosed as hyperthyroid from clinical observations, a sup-

ssed thyroid lobe, and a serum T₃ of 200 nanog/100 ml. The sixth case was thought to be hypothyroid on a clinical basis (sluggishness), the absence of any visible thyroid I131 take on scan, and a serum T₃ of 30 nanog/100 ml. The remaining dogs were thought to be euthyroid. On microscopic examination, all carcinomas had a predominantly compact cellular pattern, containing follicles ranging from rare to moderate in number. All responded to thyroid-stimulating hormone (TSH) in vitro by increasing the ³²P incorporation to phosphatides. However, in the fourth case, this did not reach statistical significance because of the large standard error of the means. The phospholipids of the fifth and sixth cases were fractionated and demonstrated an increase primarily in phosphatidylinositol and phosphatidic acid specific activity in response to TSH. Microscopic examination of incubated slices of the first four cases showed no discernible difference in morphology between those exposed to TSH and those not exposed. Colloid droplets could be observed in some of the microfollicles, but there was no visible change in their number in response to TSH. These studies show that a malignant tumor may still retain at least one complete control system extending from TSH receptors to the final metabolic response. (10 refs.)

77-1200 Differences in Production of Solid Landschutz Tumours in Balb/c and ICR Mice. (Eng.) Hod, I. (Hebrew Univ. Jerusalem, Rehovot 76-100, Israel) Zimber, A.; Gidoni, D.; Shaul, Y. *Lab Anim* 11(1): 51-52; 1977.

Adult female Balb/c and ICR mice received inoculations of Landschutz tumors in ascitic form, either sc or, for peritoneal wall tumors, ip. The sc tumors grew progressively in 35/40 ICR mice but in only 1/45 Balb/c mice. In 15 Balb/c mice the tumors were < 10 mm²; in 30 mice, they were 15-220 mm² (mostly 30-80 mm²) by days 7-12. By day 40, 44/45 Balb/c mice showed complete tumor regression, in contrast to 5/40 ICR mice. Peritoneal wall tumors grew progressively in both strains. Thus, there is a significant difference in the transplantability of the Landschutz tumor in these strains. In ICR mice the peritoneal wall tumors were more invasive than those in Balb/c mice, but their continued growth in both strains indicates that there is a difference in resistance according to site as well as strain. The skin and sc tissue may play a role in the immune reaction. (3 refs.)

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ABBREVIATIONS

JOURNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		

REVIEW

- 77-1201 **Workshop on Short-Term Carcinogenicity Testing.** (Eng.) Harnden, D. (Univ. Birmingham, Birmingham, England) *Br J Cancer* 34(6): 674-675; 1977.

The present status of short-term tests for carcinogens is discussed. Since short-term tests determine only the potential of a compound as a mutagen or carcinogen, and not the nature and level of exposure, tiered testing was suggested. This consists of simple preliminary screens followed by complex tests in animals and, ultimately, tests on man. Bacterial tests, chromosome-based tests, the DNA repair test, the dominant lethal test in mice, cellular transformation, and the 2-hydroxylation of biphenyl are discussed. The concept of acceptable risk and the legislative regulation of suspected carcinogens in Britain are mentioned. (no refs.)

- 77-1202 **The Use of the *S. Typhimurium* Mutation Assay and Cell Transformation in Vitro as Short-Term Carcinogen Tests to Monitor the Structural Inactivation of Known Carcinogens and to Detect Potential Carcinogenicity in New Compounds (Meeting Abstract).** (Eng.) Ashby, J. (Christie Hosp., Manchester, England) Paton, D.; Styles, J. A.; Anderson, D.; Longstaff, E. *Mutat Res* 46(3): 204-205; 1977. (no refs.)

- 77-1203 **In Vitro Mutagenesis Assays as Predictors of Chemical Carcinogenesis in Mammals.** (Eng.) Brusick, D. J. (Dept. Genetics Litton Bionetics, Incorporated, Kensington, MD) *Clin Toxicol* 10(1): 79-109; 1977.

The principles of in vitro mutagenesis assays used to detect mammalian carcinogens are reviewed. Discussion is made of metabolic activation by mammalian microsomes, false negatives and false positives, the techniques, advantages, and limitations of the methods, and the functional relationship between carcinogenesis and mutagenesis. The correlation between mutagenicity in vitro and carcinogenicity for a large number of chemicals is approximately 0.9. The best correlation exists for carcinogens that are themselves highly electrophilic or produce electrophilic metabolites. The correlation for hormonal, metallic, or physical carcinogens has been disappointing but not unexpected, based on their proposed mechanisms of action. In vitro assays can be conducted using activation systems derived from the tissues of any mammalian species. This permits an assessment of phylogenetic extrapolation by comparison of the metabolic activation capabilities of tissues from different species, including humans. The advantages of mutagenicity testing are the short period of time required for results, the high sensitivity of the assay, and the fact that the active species can be detected biologically without prior chemical identification and isolation. (85 refs.)

- 77-1204 **Chemical Carcinogenesis in Tissue Culture: Criteria and Tests of Transformation.** (Fre.) Chouroulinkov, I. (Institut de Recherches Scientifiques sur le Cancer-CNRS, 7, rue Guy Mocquet, B.P. no 8, 94800 Villejuif, France) Lasne, C. *INSERM* 52: 207-227; 1976.

Four criteria for evaluating cell transformation in vitro by chemical carcinogens are defined, and experimental evidence establishing the criteria is reviewed. The first criterion is cytological modification of cells in culture, which is not suitable for quantitative study of cell transformation. The second is formation of foci of abnormally growing cells, particularly cells that have lost contact inhibition. The number of atypical colonies determines the transforming activity of the carcinogen. The method has been reproduced in the laboratory using polycyclic hydrocarbons such as benzo(a)pyrene. When 30 more complex substances, such as condensations of cigarette smoke, were tested, no transformation occurred. It is concluded that this criterion is suitable for pure substances only. Formation of colonies in agar is the third criterion. Cells transformed by viruses or chemicals will form colonies in semiliquid medium such as agar, whereas normal cells will not. Agar colony formation was observed only after long-term passage of cell cultures. Agar colony formation occurred before the cells produced tumors in experimental animals. The fourth criterion is formation of tumors when cells are injected into animals. In vivo carcinogenesis is the absolute criterion of malignant cell transformation. Experiments correlating agar colony formation and tumor induction as evidence of transformation of rat embryo cells in vitro by benzo(a)pyrene are described. (41 refs.)

- 77-1205 **Retinoids and Carcinogenesis.** (Eng.) Sporn, M. B. (Lung Cancer Branch, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014) *Nutr Rev* 35(4): 65-69; 1977.

Discussion is made of the role of vitamin A and its analogs, the retinoids, in facilitating the differentiation of epithelial cells and in carcinogenesis. Retinoid deficiency enhances susceptibility to carcinogenesis by a variety of stimuli, including exposure to polycyclic hydrocarbons, nitrofurans, and aflatoxin B₁, in several tissues. These include the respiratory tract, bladder, and colon of the rat and the respiratory tract of man. Pharmacological administration of vitamin A and its synthetic analogs has been used successfully to prevent cancer of the skin, lung, bladder, and breast in experimental animals in which the dietary intake of vitamin A would have been considered adequate for most nutritional purposes. Retinyl methyl ether administered to rats in their diet 1 wk after a single oral dose of 7,12-dimethylbenzanthracene delayed the occurrence and reduced the incidence of subsequent mammary cancer. The inhibitory effects were not the result

of inhibition of the initiation of carcinogenesis, but of the progression of premalignant states of the disease to invasive malignancy. The future practical use of these agents for cancer prevention in man will depend upon the availability of appropriate synthetic retinoids. (41 refs.)

77-1206 Modifying Effects in Chemical Mutagenesis (Meeting Abstract). (Eng.) Dubinin, N. P. (Inst. General Genetics, USSR Acad. Science, Moscow, USSR) *Mutat Res* 46(3): 190-191; 1977. (46 refs.)

77-1207 Mutagenicity of Chemical Carcinogens (Meeting Abstract). (Eng.) de Serres, F. J. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC) *Mutat Res* 46(3): 190; 1977. (no refs.)

77-1208 A Suggestion Concerning the Role of the L-Region in Carcinogenesis by Polycyclic Hydrocarbons (Letter to Editor). (Eng.) Memory, J. D. (Sch. Physical and Mathematical Sciences, North Carolina State Univ., Raleigh, NC 27607) *Int J Quantum Chem* 11(1): 179; 1977.

The K- and L-region hypothesis on the carcinogenic potential of the polycyclic aromatic hydrocarbons states that in order for a polycyclic hydrocarbon to be carcinogenic it must have an active K-region and an inactive L-region. It has been shown that K-region epoxides of carcinogenic polycyclic hydrocarbons intercalate in DNA and act as frameshift mutagens. The requirement that a polycyclic hydrocarbon have an inactive L-region may be due to the fact that an addition reaction across the L-region could impair the ability of the molecules to intercalate in DNA. (5 refs.)

77-1209 Toxic Levels (Letter to Editor). (Eng.) Lijinsky, W. (Frederick Cancer Res. Center, Frederick, MD) Jukes, T. H. *Nature* 266(5602): 494; 1977.

Opposing viewpoints concerning the use of food additives found to be carcinogenic in test animals are presented. The extrapolation of animal data to humans and the possible cumulative effects of carcinogenic substances are discussed. It was suggested that consumers be given the right to decide if they want to use a product containing a substance which causes cancer in experimental animals. (6 refs.)

77-1210 Modification by Fiber of Toxic Dietary Effects. (Eng.) Kritchevsky, D. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104) *Fed Proc* 36(5): 1692-1695; 1977.

Studies of the influence of diet on the response of rats and mice to carcinogens, toxic chemicals, and infectious agents are summarized. Increases in dietary fiber had a protective effect against x-irradiation and dietary 2-acetylaminofluorene, 2,5-di-*t*-butylhydroquinone, cadmium, sodium cyclamate, amaranth, and nonionic surface active agents. However, fiber did not protect animals against pneumococcal infection or the hepatomegaly effects of ethyl-*p*-chlorophenoxyisobutyrate. (17 refs.)

77-1211 Nitrogen Intake and Tumorigenesis in Rats. (Eng.) Anonymous (No affiliation given) *Nutr Rev* 35(4): 80-82; 1977.

A report is presented of an investigation into the occurrence of tumors in groups of rats inoculated with 15 mg/kg of the carcinogen 1,2-dimethylhydrazine (DMH) and fed different dietary regimens. Adenocarcinomas of the small and large intestine were larger in gross appearance and significantly more numerous in rats fed 15% and 22.5% dietary protein (as casein) than in animals fed 7.5% protein. The concentration of ammonia in the cecal contents increased as dietary protein increased. Animals inoculated with DMH had significantly higher concentrations of ammonia in both the colon and cecum than controls. Dietary urea did not increase this concentration further. It is concluded that the time of appearance, size, and incidence of tumors are influenced by the level of dietary protein intake and that ammonia has no apparent role in tumor etiology. Ear tumors were also observed in DMH-treated rats. Rats fed 22.5% protein were first to show ear tumors (after 21 wk), but all rats eventually produced these keratin-producing papillomas of the sebaceous glands of the external ear. (7 refs.)

77-1212 Relationship Between Human Teratogens and Carcinogens. (Eng.) Miller, R. W. (Clinical Epidemiology Branch, NCI, NIH, Public Health Service, U.S. Dept. Health, Education and Welfare, Bethesda, MD 20014) *J Natl Cancer Inst* 58(3): 471-474; 1977.

Clinical observations on the relation between human cancer and genetically induced or idiopathic congenital malformations have provided new insights into the carcinogenic process. No corresponding increment in understanding has come from studies of the ability of environmental teratogens to induce cancer in man. Although alcohol, diphenylhydantoin, diethylstilbestrol, androgens, and ionizing radiation are both carcinogenic and teratogenic, they affect dissimilar organs through apparently dissimilar biologic processes. (54 refs.)

77-1213 Information for Physicians. Vaginal and Cervical Cancers and Other Abnormalities Associated with Exposure in Utero to Diethylstilbestrol and Related

Synthetic Hormones. (Eng.) DESAD Project (Office Cancer Communications, Dept. 123, Building 31, Room 10A19, NCI, NIH, Bethesda, MD 20014) *Int Surg* 62(3): 152-155; 1977.

Vaginal and cervical cancers and other abnormalities associated with exposure in utero to diethylstilbestrol (DES) and related synthetic hormones are discussed. More than 80% of the vaginal adenocarcinoma patients listed in the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females are known to have been exposed to DES-type hormones. Most of the vaginal and cervical cancers in the exposed females are associated with vaginal adenosis, a rare condition in unexposed young women. More than one-third of those exposed in the first 4 mo of gestation developed vaginal adenosis and more than two-thirds developed cervical ectropion. Young women who have been exposed to DES-type drugs should receive a thorough pelvic examination, and they should be followed on a regular basis. After an initial examination, annual pelvic examinations with cervical and vaginal cytology and iodine staining should be adequate. Treatment of cervical and vaginal cancers involves both surgery and high-energy radiotherapy. Treatment is best accomplished by physicians experienced in treating gynecologic cancers, and it should be highly individualized. (14 refs.)

77-1214 **Stilboestrol and Human Cancer.** (Eng.) Bishun, N. P. (Tissue Culture and Cytogenetics Unit, Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England) Smith, N. S.; Williams, D. C. *Clin Oncol* 3(1): 75-80; 1977.

Studies of the association between diethylstilbestrol (DES) and human cancer are reviewed. There is no doubt that a causal relationship exists between in utero exposure to DES and the later development of vaginal carcinoma in young women. The critical period of exposure is the eighth week of pregnancy, when the rudiments of the female lower genital tract are involved in organogenesis. One study has drawn attention to the apparent increase of uterine corpus, prostatic, testicular, and male bladder cancer among young people from 1950 to 1962 and 1963 to 1969, but there is no evidence that maternal treatment with DES contributed to the development of tumors other than those of the lower female genital tract. The changes leading to clear-cell adenocarcinoma of the genital tract that have been observed in the young women suggest that there is a disturbance in the interplay of Mullerian and urogenital sinus epithelium early in intrauterine life. The occasional occurrence of transverse vaginal cervical ridges in exposed patients with or without cancer shows that DES may have a teratogenic as well as a carcinogenic effect. (21 refs.)

77-1215 **ATA Statement on Breast Cancer and Thyroid Hormone Therapy.** (Eng.) Gorman, C. A. (Education Committee, American Thyroid Association) Becker,

D. V.; Greenspan, F. S.; Levy, R. P.; Oppenheimer, J. H.; Rivlin, R. S.; Robbins, J.; VanderLaan, W. P. *J Pediatr* 90(4): 683-684; 1977.

Studies are reviewed which indicate the highly tenuous nature of a recently implied link between thyroid hormone therapy and breast cancer. Since the adverse effects of withholding such therapy in patients with hypothyroidism are unquestioned, it is recommended that patients taking thyroid hormones for well-established indications continue their medication. (28 refs.)

77-1216 **Cancer and Hair Dyes (Letter to Editor).** (Eng.) Menkart, J. (Clairol Inc., 2 Blachley Road, Stamford, CT 06902) Lanman, B. M. *NY State J Med* 77(3): 366; 1977.

Evidence that carcinogenic polycyclic hydrocarbons are a hazard in hair dyes is refuted. None of the products used in hair dyes are structurally related to these compounds, although some hair dye intermediates are aromatic amines. Hair dyes have not been shown to contain known carcinogens, nor have epidemiological studies shown an increase in breast cancer accompanying increased use of hair dyes. (6 refs.)

77-1217 **Cancer and Hair Dyes (Letter to Editor).** (Eng.) Shafer, N. (10 East 85th St., New York, NY 10028) Shafer, R. *NY State J Med* 77(3): 366, 340, 344; 1977.

Various studies are cited to illustrate that components of hair dyes can be both carcinogenic and mutagenic. These substances are absorbed through the skin, as indicated by a study of the urine, and thus are not detoxified by the digestive system or liver. It may take some time before a corresponding increase in breast cancer is demonstrated. (14 refs.)

77-1218 **American Thyroid Association Statement: Breast Cancer and Thyroid Hormone Therapy.** (Eng.) Gorman, C. A. (Education Committee, American Thyroid Association) Becker, D. V.; Greenspan, F. S.; Levy, R. P.; Oppenheimer, J. H.; Rivlin, R. S.; Robbins, J.; VanderLaan, W. P. *Ann Intern Med* 86(4): 502-503; 1977.

Various studies dealing with the relationship between thyroid hormone therapy and breast cancer are reviewed. Because of conflicting results, it is suggested that patients who are taking thyroid medication should continue to do so and that studies be designed to investigate any possible relationship. (28 refs.)

77-1219 **Maleic Hydrazide: Should the Delaney Amendment Apply to its Use?** (Eng.) Haley, T. J.

(Dept. Health, Education and Welfare, Food and Drug Admin. Natl. Center Toxicological Res., Jefferson, AR 72079) *J Toxicol Environ Health* 2(5): 1085-1094; 1977.

The chemistry, metabolism, toxicology, mutagenicity, and carcinogenicity of maleic hydrazide (MH) are reviewed. MH is mutagenic and carcinogenic in cell cultures and animals, but no evidence is available of carcinogenicity in humans. Populations exposed to MH in manufacturing, agriculture, and in the diet should be surveyed. Long-term ingestion experiments in several animal species are needed to establish whether MH is carcinogenic by this route. Biotransformation and pharmacokinetic studies are suggested for the study of MH metabolism and excretion. Such investigations would firmly establish whether the use of MH should be banned under the Delaney Amendment, which prohibits the use of food additives which have not been adequately tested to establish their safety. (66 refs.)

77-1220 Occupational Disease. When the Workplace is the Etiology. (Eng.) Liggins, M. R. (No affiliation given) Denson, L. J.; Napolitano, L. V.; Salvaggio, J.; Stopford, W. *Patient Care* 11(5): 108, 113, 117, 119, 123, 125-128; 1977.

An overview of chemicals, heavy metals, and inhalants which may cause occupation-associated illnesses is presented. Lung toxins, carcinogens, acute respiratory disorders, and chronic toxicity are discussed. Home exposure to agents such as paint thinner, degreasing compound and hair spray are also discussed. A diagnostic approach for the determination of an occupation-caused illness is presented. (15 refs.)

77-1221 Comment on Methodology and Interpretation of Results (Letter to Editor). (Eng.) Kapadia, G. J. (Dept. Biochemical Chemistry, Coll. Pharmacy and Pharmaceutical Sciences, 2300 4th St., N.W., Washington, DC 20059) Chung, E. B.; Pradhan, S. N. *J Natl Cancer Inst* 58(3): 476-477; 1977.

The use of the sc administration method is defended as valid for studying the carcinogenic potential of plant materials, including tannin fractions, in rats. The tumors induced were correctly diagnosed by pathologists as malignant fibrous histiocytomas. (12 refs.)

77-1222 Comment on Methodology and Interpretation of Results (Letter to Editor). (Eng.) Pelfrene, A. F. (Dept. Pathology-Toxicology, Searle Lab., Box 4110, Chicago, IL 60680) *J Natl Cancer Inst* 58(3): 475-476; 1977.

The use of the sc injection technique is criticized as a method for determining the carcinogenicity of plant extracts, includ-

ing tea. Evidence that the carcinogenic action of a chemical cannot be assessed from its ability to induce sc sarcomas in rats is reviewed. (16 refs.)

77-1223 Review of the Use of Radioactive Materials in Dishware (Meeting Abstract). (Eng.) Simpson, R. E. (Bureau Radiological Health, Food and Drug Admin., Rockville, MD 20857) *Radiat Res* 70(3): 666; 1977. (no refs.)

77-1224 Irreparable DNA Damage by Industrial Pollutants in Premature Aging, Chemical Carcinogenesis and Cardiac Hypertrophy: Experiments and Theory (Meeting Abstract). (Eng.) Acharya, P. V. (Industrial Safety and Health Inst., Univ. Wisconsin, Madison, WI) *Isr J Med Sci* 13(4): 441-442; 1977. (no refs.)

77-1225 Early Detection of Breast Cancer: Benefit Versus Risk. (Eng.) Humphrey, L. J. (70 Terrace Trail East, Quivira Lake, KS 66106) *Am J Surg* 133(3): 265-266; 1977.

The use of mammography for the detection of breast cancer is advocated for screening asymptomatic women under 50 yr of age as well as for traditionally high risk groups, and statistics are reviewed in support of this contention. It is suggested that the benefits of diagnostic low dose radiation outweigh the dangers, especially since cellular reparative processes may compensate for the alleged cumulative effects of radiation. (3 refs.)

77-1226 Review Article. Potential Hazards of Diagnostic Radiation. (Eng.) Houston, C. S. (Dept. Diagnostic Radiology, Univ. Hosp., Saskatoon, Saskatchewan, S7N 0W8, Canada) Shokeir, M. H. *J Can Assoc Radiol* 28(1): 62-68; 1977.

The extent of damage from small doses of diagnostic radiation cannot be determined precisely, but this review article discusses what is known about the major radiation risks, ie, damage to the fetus, carcinogenesis, and genetic damage. Damage to the fetus may include the following: death of the zygote, growth retardation (usually not a matter of concern with small doses) and teratogenesis. Certain brain and eye abnormalities, of which microcephaly is the most common, are the only documented fetal abnormalities that have resulted from irradiation of pregnant women. There is suggestive evidence from one study that intrauterine radiation may cause a type of leukemia that is more resistant to treatment. An increased cancer risk has been seen in persons irradiated for thymic enlargement as children, in patients receiving radi-

um for benign diseases, in patients fluoroscoped for artificial pneumothorax, and in survivors of the atomic bomb in Hiroshima and Nagasaki. Genetic damage from diagnostic radiation is also difficult to estimate. Diagnostic radiation of females, even in childhood, may be related to an increased incidence of Down's syndrome (in the offspring) in older mothers. Radiation also causes point mutations, which may explain the increase of some genetic abnormalities in the children of older fathers. The possibility of causing genetic damage is a major reason for using radiation wisely and in moderation, especially in pregnant women, children, and in men and women throughout the reproductive period. (53 refs.)

77-1227 Radiation Therapy for Pertussis: A Possible Etiologic Factor in Thyroid Carcinoma (Letter to Editor). (Eng.) Webber, B. M. (Dept. Radiation Oncology, Rhode Island Hosp., Providence, RI 02902) *Ann Intern Med* 86(4): 449-450; 1977.

The possibility is raised that hundreds of adults may be at risk for developing thyroid carcinoma as a result of radiation given in infancy and childhood for whooping cough. The literature relating to such treatment is reviewed. (4 refs.)

77-1228 DNA Repair -- Cellular Level (Meeting Abstract). (Eng.) Harnden, D. G. (Univ. Birmingham, Dept. Cancer Studies, The Medical Sch., Birmingham B15 2TH, England) *Mutat Res* 46(2): 124-125; 1977. (no refs.)

77-1229 Nuclear Energy: Technical and Human Aspects. (Fre.) Paskievici, W. (Institut de genie nucleaire, Ecole Polytechnique de Montreal, Montreal, Canada) *Ingenieur* 62(315): 25-34; 1976.

The risk of environmental pollution by nuclear energy plants through release of radiation, heat, or chemicals is reviewed. Humans are exposed to radiation from natural sources at far higher levels than those produced by nuclear power plants. Nevertheless, a max additional dose of radiation [0.17 rem (roentgen-equivalent-man)/yr] from nonnatural sources has been defined by international consensus. The annual radiation dose for the av inhabitant of the US is 0.182 rem (natural, 0.106; medical, 0.73; other, excluding nuclear energy, 0.03). It has been calculated that 1,000 nuclear reactors in the US would add an av dose of 0.1 millirem/yr to the present radiation received by each inhabitant plus several tenths of a millirem from the reprocessing of radioactive waste. The risk of radioactive contamination from an accidental malfunction of an energy plant is considered. According to a table reproduced from a US government report, the risk of an accident that would kill 1 individual, injure 300, and produce an av

of 170 deaths/yr for 30 yr and 25 genetic modifications/yr for a total of 3,000 is about 1/1 million yr of reactor operations. Safe disposal of radioactive wastes is discussed. Finally, the risks incurred from energy produced by other means are compared to those of nuclear energy. (26 refs.)

77-1230 Chromosomes and Malignancy (Meeting Abstract). (Eng.) Harnden, D. G. (Dept. Cancer Res. Univ. Birmingham, Birmingham, England) *J Clin Pathol* 29(11): 1043; 1976. (2 refs.)

77-1231 Sipple Families. (Eng.) Anonymous (No affiliation given) *Lancet* 1(8018): 939-940; 1977.

Sipple's syndrome, a familial syndrome consisting of parathyroid adenoma, pheochromocytoma, and medullary carcinoma of the thyroid, is one of the multiple-endocrine-adenomatosis syndromes, with an autosomal dominant mode of inheritance. In patients with medullary carcinoma of the thyroid (MCT), there is a 14-fold increase in the frequency of pheochromocytoma. MCT is rare, but when it does occur it is often part of the Sipple syndrome. Diagnostic screening and treatment of Sipple families are discussed. Genetic counselling for affected persons is a must, as each of their offspring has a 50% risk of inheriting the gene. (20 refs.)

77-1232 Epidemiology of Hodgkin's Disease in the Young. (Eng.) Gutensohn, N. (Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Avenue, Boston, MA 02115) Cole, P. *Int J Cancer* 19(5): 595-604; 1977.

Epidemiological data on Hodgkin's disease (HD) among adolescents and young adults are reviewed in terms of the possible infectious etiology of the disease. The Epstein-Barr virus has been studied in connection with HD, and it has been suggested that HD is a contagious disease that can be transmitted by patients or their close contacts. An alternative infectious disease model based on analogy with paralytic poliomyelitis (PP) is proposed. Like PP, HD may be a rare manifestation of a common infection. Disease risk is greatest among young children from the least favorable environment, but greatest among adolescents and young adults from the most favorable environment. According to this model, HD patients represent no hazard to their contacts; however, the incidence of HD among young adults may increase in the coming decade because of the current high standard of living and small family size. (104 refs.)

77-1233 RNA Tumor Viruses. A State-of-the-Art Report. (Fre.) Jolicoeur, P. (Laboratoire de biologie moleculaire, Institut de recherches de Montreal, 110 ou-

est, avenue des Pins, Montreal, Quebec, Canada) *Union Med Can* 106(4): 577-584; 1977.

The principal aspects of RNA tumor viruses, including morphology, genetic organization, intracellular replication, and homology, are reviewed. A table showing the classification of the RNA oncogenic viruses according to whether they are C-, B- or other types is included. The complexity of the genetics of RNA viruses is illustrated by the murine leukemia and sarcoma viruses. Data on RNA tumor viruses in humans are summarized: certain viral markers such as DNA polymerase and RNA and DNA viral sequences have been demonstrated in human cancer cells, and the isolation of C-type RNA tumor viruses from cultured human leukemia cells has been reported. (94 refs.)

- 77-1234 Organization of the Genomes of Polyoma Virus and SV40.** (Eng.) Fried, M. (Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London, England) Griffin, B. E. *Adv Cancer Res* 24: 67-113; 1977.

The organization of the genetic information within the polyoma virus and simian virus 40 (SV40) genome is reviewed. Both of these papovaviruses will cause tumors in various rodents in vivo. Polyoma virus will transform some types of rodent cells and, in tissue-culture systems, SV40 will also transform monkey and human cells. Although both have a remarkable organizational similarity, they show limited sequence homology and different host-range properties. They differ with respect to the cells they transform as well as to their so-called lytic properties. Mouse cells are "permissive" for lytic infection with polyoma virus, monkey cells for SV40. The genetic information of both polyoma virus and SV40 resides in their DNA's, which have molecular wts of about 3.4×10^6 daltons. The early and late regions each comprise about 50% of the genome, and the genes specifying the early proteins are distributed similarly in both viral DNA's. Physical maps are given for these DNA's. (241 refs.)

- 77-1235 The Fractionation and Characterization of the Low Molecular Weight RNA of RNA Tumor Viruses.** (Eng.) Peters, G. G. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 13-25; 1976.

Fingerprint analysis was used to study the low molecular wt RNA's of RNA tumor viruses. The pattern of oligonucleotide spots obtained by fingerprinting is characteristic of the nucleotide sequence of the particular RNA. Furthermore, the number of spots serves as an indication of purity. Fingerprint analysis is a rapid and simple means of structural characterization, and it permits one to decide whether RNA's isolated from two different sources are identical, at least at the level of the primary sequence. It is possible to identify which oligonucleotide on a fingerprint corresponds to the anticodon

by doing fingerprints with and without pretreatment with S₁ nuclease. The advantage is that only one oligonucleotide need be fully sequenced to deduce the anticodon. The methodology is generally applicable, possibly with slight modification, to most size and functional classes of RNA, hopefully including immune RNA. (23 refs.)

- 77-1236 Cancer Immunology.** (Eng.) Old, L. J. (No affiliation given) *Sci Am* 236(5): 62-79; 1977.

The principles of cancer immunology are discussed with particular reference to murine experimental systems. Experiments with inbred mouse strains have demonstrated that chemically induced tumors consistently elicit immunity to themselves but not to any other tumors, indicating that different antigens are expressed even when the tumors have been elicited by the same chemical agent in the same strain. Conversely, identical antigens appear in different tumors induced by the same virus. Naturally occurring murine tumors have generally been found to be only weakly antigenic and, in certain cases, not antigenic at all. Discussion is also made of the serological investigation of tumors, leukemia antigens (in particular, those of murine leukemia virus), mechanisms of escape from immunological surveillance, the immunotherapy of cancer, and immunopotentiators such as BCG and endotoxin. (no refs.)

- 77-1237 Immunological Aspects of Cancer Etiology.** (Eng.) Murphy, S. G. (Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX) *Cancer Bull* 28(3): 5-9; 1976.

In this review of immunology and cancer etiology, an attempt is made to determine whether: (1) the immune system eliminates new malignant cells from the host; (2) an imbalance of the immune system leads to an increased incidence of malignancy; or (3) the deviation of controlling mechanisms leads to the development of malignant clones within the lymphoreticular system. Genetic factors have been shown to influence the susceptibility of animals to develop neoplasms. One study demonstrated that unless genetic factors permitting the action of an oncogenic agent are present, immunosuppression has no effect. In certain inbred mouse strains, suppression of cellular immunity enhanced tumor formation. Immunosuppression may decrease the development of carcinogen-induced malignancy. It is suggested that, under certain conditions, the immune response may facilitate tumor formation. In man, altered states of immunity can occur congenitally (immunodeficiency syndromes) or as a result of immunosuppressive therapy. Clinically, there is an increased incidence of malignancy in immunologically compromised patients. Current data show that a subclass of T lymphocytes, suppressor T cells, normally controls humoral and cellular functions. The decline of these cells or their products may result in autoimmune disorders. (5 refs.)

77-1238 Relationship of Causative Factors in Spontaneous Regression of Cancer to Immunologic Factors Possibly Effective in Cancer. (Eng.) Cole, W. H. (8 W. Kensington Road, Asheville, NC 28804) *J Surg Oncol* 8(5): 391-411; 1977.

Various reactions associated with therapeutic regression of cancers in human beings were reviewed in an attempt to develop a correlation between this type of regression and spontaneous regression. A total of 176 cases of spontaneous regression were collected from the literature for 1900-1964. It appears that a stimulation of the immune process might explain most of the regressions. BCG is one of the best known stimulating agents, but other bacterial agents or fractions are known to have this action. Hormonal changes might also be responsible for some of the regressions. Theoretically, humoral immunity against tumor antigens should be the most effective method of developing immunity, but results have been disappointing. Humoral tumor immunity has been divided into three basic types: (1) cytotoxic or nonblocking antibody; (2) enhancing or blocking antibody; and (3) cytostatic antibodies. Immunoglobulins (Ig's) appear to be related to growth and resistance to malignancy, but more data are required to determine the significance of the changes in levels of the various Ig's. Levamisole given at the time of resection of the lung because of carcinoma has been reported to improve patient survival. It is believed that the drug may prevent hematogenous spread of the tumor during surgery and/or decrease the immunosuppression caused by a major operation. Several ongoing human trials using immunotherapy as an adjuvant to high-risk Stage II melanoma are briefly discussed to illustrate the techniques and results. (80 refs.)

77-1239 Specific and Nonspecific Activation of Macrophages: Significance in Tumor Immunity. (Eng.) Evans, R. In: *Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias*. NCI and John E. Fogarty International Center for Advanced Study in the Health Sciences. (Bethesda, Maryland): pp. 295-301; 1974.

The importance of nonspecific and specific macrophage activation is evaluated. Macrophages may be rendered non-specifically cytotoxic via an immunological and nonimmunological pathway. Specific cytotoxic macrophages may be found after immunization of mice with irradiated syngeneic tumor cells or allogeneic cells. Macrophage cytotoxicity measured either by lysis or growth inhibition may be initiated by specific or nonspecific pathways. Specific cytotoxicity occurs when immune macrophages from specifically immunized mice or normal macrophages armed in vitro, either by interaction with sensitized lymphocytes or by incubation with a soluble product of antigen-stimulated sensitized lymphocytes, require interaction in a specific immunological way with the immunizing antigen before cytotoxicity is expressed. Macrophages play a significant overall role in surveillance mechanisms, possibly by amplifying other specific mechanisms.

The demonstration that activated macrophages can be isolated from actively growing tumors and from other sources suggests that these macrophages may play a part in preventing the induction of neoplasms and in controlling tumor growth rate and, possibly, the rate of metastatic spread. (38 refs.)

77-1240 Disorders of Leukocyte Chemotaxis. (Eng.) Snyderman, R. (Div. Rheumatic and Genetic Diseases, Dept. Medicine, Duke Univ. Medical Center, Durham, NC 27710) Pike, M. C. *Pediatr Clin North Am* 24(2): 377-393; 1977.

Abnormalities of chemotaxis resulting from the following mechanisms are reviewed: (1) dysfunctions of immune recognition; (2) abnormalities of chemotactic factor production; (3) abnormal inactivation of chemotactic factors; (4) inhibition of chemotactically active cells by circulating antagonists; and (5) intrinsic cellular defects. Dialyzable transfer factor obtained from patients with Sezary's syndrome, a T-cell leukemia, is markedly deficient in chemotactic activity. Elevated levels of chemotactic factor inactivator have been implicated as the cause of cellular immunity defects in patients with Hodgkin's disease. Patients who had undergone bone marrow transplants as a treatment for aplastic anemia or leukemia had depressed neutrophil chemotaxis. This state was most frequently associated with graft-versus-host disease and the administration of antithymocyte globulin. Several studies have been made of monocyte chemotaxis in vitro in patients with cancer; and up to 50% of these patients had depressed chemotactic responses. In one study 44% of the patients with abnormal chemotaxis prior to immunotherapy died of their disease during a 1-mo to 2-yr follow-up period, but only 5% of the patients whose chemotaxis was normal died during the same period. (104 refs.)

77-1241 Beta₂-Microglobulin on the Cell Surface. (Eng.) Peterson, P. A. (Dept. Medical and Physiological Chemistry, Biomedical Center, Univ. Uppsala, Uppsala, Sweden) *Med Biol* 55(2): 74-81; 1977.

A review is presented of some of the products of the major histocompatibility complex (MHC) of the mouse, which contains the genes for the proteins responsible for graft rejection. The specific topics include the H-2K- and D-gene products, TL antigens, Ss protein, I-region defined antigens, ontogeny of MHC antigens and the evolutionary aspects of the MHC region. (42 refs.)

77-1242 Tumor Antigens Inducing Immune Reactions. (Fre.) Burtin, P. (Institut de Recherches Scientifiques sur le Cancer, Laboratoire d'Immunochimie, BP 8,

94800 Villejuif, France) *Ann Immunol (Paris)* 128C (/12): 507-516; 1977.

Experimental immunological evidence for the presence of antigens on cells from virally and chemically induced tumors is reviewed. The relationship of indigenous embryonic and histocompatibility antigens to the tumor antigens is discussed. Antigen-antibody reactions with sera of patients with Burkitt's lymphoma, malignant melanoma, osteo- and fibrosarcoma, leukemia, and colonic and rectal carcinoma and the tumor cells are discussed. It is concluded that the isolation and characterization of antigens of human tumors need to be perfected, particularly from the aspect of immunotherapy and the induction of beneficial immune reactions. (48 refs.)

77-1243 Induced Delayed Hypersensitivity Reactions in Modulating Host Resistance. (Eng.) Klein, E.; Holtermann, O. A.; Djerassi, I.; Milgrom, H.; Case, R. W.; Adler, S.; Rosner, D.; Song, S. Y. In: *Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias*. NCI and John E. Fogarty International Center for Advanced Study in the Health Sciences. (Bethesda, Maryland): pp. 195-206; 1974.

Studies of the antitumor effects of delayed hypersensitivity challenge reactions at sites of tumor involvement show that these reactions result in eradication or regression of premalignant and malignant lesions in experimental animals and in man. Antibody can confer selectivity to the cytotoxic interactions of macrophages with target cells, and activated macrophages seem to possess an inherent recognition mechanism that allows them to differentiate among various cells, including neoplastic cells. In vitro investigations of rodent peritoneal macrophages demonstrate their preferential cytotoxicity for neoplastic cells. The antitumor effects of challenge reactions elicited by haptens, microbial antigens, or lymphokine preparations are similar in different types of cancers. Tumor regression following induction of a delayed-type hypersensitivity inflammatory infiltrate at the tumor site may be associated with a local amplification of a primitive surveillance mechanism. (75 refs.)

77-1244 Strategies of Active Immunization Applicable to Cancer. (Eng.) Lindenmann, J. In: *Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias*. NCI and John E. Fogarty International Center for Advanced Study in the Health Sciences. (Bethesda, Maryland): pp. 187-190; 1974.

Three strategies to provide the tumor host with a potent immunogenic stimulus are described. In "heterogenization", an immunogen is attached in some way to the tumor cell membrane, the immune response is directed at this immunogen,

and the tumor cells are concomitantly damaged because of the immunogen's close association to the tumor cell membranes. In "flushing out", an immunogen is introduced in close vicinity to the tumor deposits, and the immune reaction thus triggered is thought to affect the tumor nonspecifically, eg, by way of activated macrophages. In "augmented immunogenicity", an immunogen is introduced so that it acts as a carrier to the tumor-associated antigen, and an immune response is induced that is at least partly directed against the antigen. Animal models, however elaborate, will provide answers only for the species involved. Strictly controlled clinical trials are needed to learn about tactics, but here it would be essential to have some means of monitoring the host's immune response toward the tumor. (11 refs.)

77-1245 An Introduction to Immune RNA. (Eng.) Crouch, R. J. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. xv-xxiii; 1976.

Cells incubated in the presence of immune RNA can be converted to the production of antibodies of the specificity of the cell from which the immune RNA is isolated. The strongest support for the concept of immune RNA is based on genetic differences among the immunoglobulins (Ig's) of different animals. A plausible explanation for the phenomenon of immune RNA is that an antigen is still present in the RNA extract, and it is the antigen that elicits the formation of antibody in lymph node cells. Immune RNA may be identical to messenger RNA for Ig's. Since myelomas produce a single species of Ig, immune RNA obtained from these tumors may transfer very specific information to the recipient cells. It may be possible to utilize immune RNA to convert cells to a new, genetically distinct, Ig type. Microinjection techniques should be significant in solving some of the problems of immune RNA biochemistry. (26 refs.)

77-1246 Current Status of Immune RNA. (Eng.) Fishman, M.; Adler, F. L. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 53-59; 1976.

A differentiation is made between two classes of RNA that have often been lumped together under the designation of immune RNA. One is informational RNA (i-RNA), which has all the characteristics of messenger RNA. The other is a complex of RNA and antigen or antigen fragments. The contention that i-RNA initiates antibody formation independently of antigen has not been readily accepted. The terms "immune RNA" or "immunogenic RNA", which are not only ambiguous but inaccurate, should be discontinued, as they convey the impression of designating one substance instead of at least two. Although the identity of i-RNA and messenger RNA has been established, many questions remain

concerning the mechanism by which such RNA finds its way to the polysomes and about the manner in which information or product is integrated into cellular RNA or protein, respectively. (27 refs.)

- 77-1247 **Transfer of Cellular Immunity with Immune RNA Extracts and Tumor Immunotherapy.** (Eng.) Dray, S. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 61-73; 1976.

The transfer of cellular immunity with RNA extracts of lymphoid tissues was examined. The RNA was extracted from the lymph nodes of patients with skin sensitive to tuberculin purified protein derivative and/or histoplasmin. In investigations with allogeneic transfer in man, when the RNA extracts were fractionated by sucrose density gradient centrifugation, cell conversion was localized to the 8S-12S fraction. Thus, the conversion of nonsensitive cells by RNA to sensitive cells required intact RNA. That the effective RNA is 8S-12S has been confirmed for monkey RNA and guinea pig RNA in two other systems. Syngeneic systems were then used to determine whether the in vivo delayed hypersensitivity skin test can be transferred by adoptive transfer of RNA-treated peritoneal exudate cells. Because the development of an immunotherapy procedure utilizing lymphoid RNA extracts in man may depend on the availability of a tumor-immunized RNA donor of another species, the possibility of transferring cellular immunity with RNA extracts across species barriers was evaluated. For the development of optimal conditions for immune RNA therapeutic procedures that may become applicable to man, the line-10 hepatoma model in the guinea pig appears highly suitable. (20 refs.)

- 77-1248 **Chemical Studies on RNA.** (Eng.) Gilham, P. T. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 3-12; 1976.

Studies on RNA have been directed toward employing the specific chemical behavior exhibited by reactive centers in the determination of the primary and secondary structure of RNA species, the isolation of specific RNA molecules and RNA fragments, and the chemicoenzymatic synthesis of polyribonucleotides. Two of the special properties of the terminal cis-diol group that can be utilized in RNA studies are its susceptibility to oxidation by periodate and its ability to form cyclic complexes with compounds containing the dihydroxyboryl group. Investigations of the fine structure of nucleic acids have depended on the availability of methods for the specific degradation of polynucleotide chains. The specific activation of the monoesterified phosphate groups of nucleic acids and polynucleotides may be used to install a chemical

handle at their terminals. The specific chemical blocking of nucleotide 2'-hydroxyl groups forms a significant aspect of a new method for the stepwise synthesis of polyribonucleotides of predetermined sequence. (51 refs.)

- 77-1249 **Ribonucleases and Factors Influencing Their Activities.** (Eng.) Crouch, R. J. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 37-43; 1976.

Studies on ribonucleases (RNases) are discussed with respect to their cellular functions and activities under different conditions in vitro, and the relationship of these activities to the stability of RNA in isolation procedures or presentation cells is evaluated. RNases can be categorized according to the structure of the RNA, base specificity, position of the phosphate residue after cleavage, and the exo- or endonucleolytic character of the enzyme. When the manner in which cells handle the problem of RNases and RNA stability is examined, the natural protection mechanism useful in other circumstances is elucidated. The properties of RNase III of *Escherichia coli* and the problems generated in determining if the enzyme has been inhibited are reviewed. Presenting the cell with RNA in some form resistant to RNases is suggested as an alternative to inhibiting all RNases. (35 refs.)

- 77-1250 **Enzymes in Cancer: The Phosphohydrolases.** (Eng.) Bodansky, O. In: *Biochemistry of Human Cancer*. Bodansky, O., ed. (New York: Academic Press, Inc.): pp. 61-92; 1975.

Acid phosphatase (AP), alkaline phosphatase and 5'-nucleotidase, enzymes used in the diagnosis and management of patients with cancer, are discussed. Patients with carcinoma of the prostate have elevation of serum AP activity. Serum AP has also been reported to be elevated in low incidence and to a slight or moderate degree in tumors with metastases to the liver or skeleton, Paget's disease, hyperparathyroidism, thrombocytosis, myeloproliferative diseases, and Gaucher's disease. The incidence of increased serum placental alkaline phosphatase activities in patients with cancer is not significantly greater than that in patients with non-neoplastic disease. However, there is an increased incidence of enzymatic activity (approx 15%) in females with genitourinary and breast tumors. Serum 5'-nucleotidase is elevated in patients with hepatic disease, but is not affected in those with skeletal disease. It appears that 5'-nucleotidase is a fairly specific indicator of hepatic disease and that, in neoplastic hepatic disease, when skeletal lesions are absent, it is often a more sensitive indicator than serum alkaline phosphatase. (133 refs.)

CHEMICAL CARCINOGENESIS

- 77-1251 **Morphological Transformation of Early Passage Golden Syrian Hamster Embryo Cells Derived from Cryopreserved Primary Cultures as a Reliable In Vitro Bioassay for Identifying Diverse Carcinogens.** (Eng.) Pienta, R. J. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD 21701) Poiley, J. A.; Lebherz, W. B. *Int J Cancer* 19(5): 642-655; 1977.

Cryopreserved primary cultures of golden Syrian hamster embryo cells were successfully used as the source of target and feeder cells for establishing an in vitro carcinogenesis bioassay. The primary culture pretested before freezing continued to give positive results when retested repeatedly with 3-methylcholanthrene after cryopreservation. Susceptible positive cultures were used to test a large number of carcinogenic and noncarcinogenic chemicals. The results showed a very high positive correlation (90.8%) between morphological transformation and the reported carcinogenic activity of the chemicals. Those few carcinogens that did not produce observable transformation may not be metabolized to their active forms by early passage hamster embryo cells; N-2-acetylaminofluorene transformed cells only when hamster liver microsomes were added. No false positive results were obtained with noncarcinogens, nor was spontaneous transformation observed in control cultures. Cultures derived from morphologically transformed colonies arising after treatment of cells with several known carcinogens were tumorigenic in vivo, demonstrating the validity of altered morphology as an in vitro criterion for carcinogenicity in vivo. (19 refs.)

- 77-1252 **Role of DNA Repair in the Cytotoxic and Mutagenic Action of UV Radiation and Chemical Carcinogens in Normal and Xeroderma Pigmentosum Cells (Meeting Abstract).** (Eng.) Maher, V. M. (Biology Dept., Michigan Cancer Foundation, Detroit, MI 48201) McCormick, J. J. *Mutat Res* 46(2): 139-140; 1977. (no refs.)

- 77-1253 **Induction of Unscheduled DNA Synthesis by Chemical Mutagens in Spermatogenic Cells of the Mouse in Vitro (Meeting Abstract).** (Eng.) Beikirch, H. (Zentrallaboratorium für Mutagenitätsprüfung der Deutschen Forschungsgemeinschaft, D-7800 Freiburg, W. Germany) *Mutat Res* 46(3): 210-211; 1977. (no refs.)

- 77-1254 **Comparison of DNA Damaging Activity of Chemical Mutagens and Carcinogens in Bacteria with Different DNA Repair Capacities (Meeting Abstract).** (Eng.) Braun, R. (Zentralinstitut für Genetik und

Kulturpflanzenforschung der Akademie der Wissenschaften der DDR, 4324 Gatersleben, E. Germany) Zander, M.; Adler, B. *Mutat Res* 46(3): 214; 1977. (no refs.)

- 77-1255 **Use of Sister Chromatid Exchange Techniques for Cytological Detection of Mutagen Carcinogen Exposure (Meeting Abstract).** (Eng.) Perry, P. (MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh, EH4 2XU, Scotland) *Mutat Res* 46(3): 205; 1977. (no refs.)

- 77-1256 **Measurement of "Unscheduled" Synthesis in HeLa Cells by Liquid Scintillation Counting after Carcinogen Treatment.** (Eng.) Martin, C. N. (Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England) McDermid, A. C.; Garner, R. C. *Cancer Lett* 2(6): 355-360; 1977.

Liquid scintillation counting was used to detect DNA repair in HeLa cells following treatment with a carcinogen. The HeLa cells were conditioned in a medium deficient in arginine to reduce S-phase DNA synthesis. They were then treated with either N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), 7-bromomethylbenz(a)anthracene (BrMBA), N-acetoxy-2-acetylaminofluorene (N-acetoxy-AAF), or ethyl methanesulfonate (EMS). DNA synthesis occurred in all cells treated with a carcinogen, as shown by the incorporation of ³H-thymidine. In a parallel experiment using mouse L cells and N-acetoxy-AAF, no unscheduled DNA synthesis was observed. Aflatoxin B₁ induced low levels of repair that were greatly increased by the addition of liver stock solution (0.5 ml, containing 0.2 ml 25% liver post-mitochondrial fraction, 0.2 ml glucose-6-phosphate (60 mg/ml), 0.1 NADP (25mg/ml) and 0.1 ml 160mM MgCl₂). The results suggest the usefulness of this procedure in screening for chemical carcinogens. (15 refs.)

- 77-1257 **Induction of Micronuclei in Mouse and Hamster Bone-Marrow by Chemical Carcinogens.** (Eng.) Friedman, M. A. (Dept. Pharmacology, Medical Coll. Virginia, Health Sciences Div., Virginia Commonwealth Univ., Richmond, VA 23298) Staub, J. *Mutat Res* 43(2): 255-261; 1977.

Four carcinogens, dimethylnitrosamine (DMN), 3-methylcholanthrene (3-MC), acetylaminofluorene (AAF), and aflatoxin B₁ (AFB₁) were tested in the micronucleus test using mice (acute tests) and hamsters (acute and subacute

sts). Male and female Swiss mice (DUB:ICR) and male golden Syrian hamsters were used. The compounds were administered ip 30 and 6 hr prior to killing (in the acute tests). In the subacute tests, the compounds were administered three times per wk for 1 to 12 wk. Animals injected with triethylenemelamine were used as controls. 3-MC induced a dose-dependent increase in the number of micronuclei, yielding a 2.65-fold increase over controls at a dose of 60 mg/kg. At 1,000 and 2,000 mg/kg AAF, the incidence of micronuclei showed 3.0- and 5.04-fold increases, respectively. The bone marrow depression (RBC/nucleated cells) was 38.9% at 1,000 mg/kg AAF and 53.7% at 2,000 mg/kg. At 15 and 20 mg/kg, AFB₁ increased the incidence of micronuclei by 1.65- and 1.67-fold, respectively. No bone marrow toxicity was observed with AFB₁. With DMN, considerable bone marrow toxicity was seen beginning at 14 mg/kg, and mortality was seen at 50 mg/kg. At 2 mg/kg DMN, there was a 1.48-fold increase in the number of micronuclei; this reached a maximum of 2.89-fold at 14 mg/kg. In hamsters, all of the test compounds except AFB₁ increased the percentage of micronuclei. The data indicate that the environmental carcinogens tested were all active in the micronucleus test. Therefore, bone marrow toxicity must be considered during evaluations of the mutagenic activity of carcinogens with the micronucleus test. The micronucleus test did not appear useful in chronic protocols, but the acute studies showed that this procedure is of value in the characterization of the mutagenic potential of a compound. (7 refs.)

77-1258 **Synthesis and Conformation of Dinucleoside Monophosphates Modified with Aromatic Residues: An Extension of the Base Displacement Theory of Carcinogenesis** (Meeting Abstract). (Eng.) Shapiro, R. (Dept. Chemistry, New York Univ., New York, NY 10003) Brown, S. S. *Fed Proc* 36(3): 695; 1977. (no refs.)

77-1259 **Genetic Susceptibility to Chemical Carcinogenesis from Aromatic Amines** (Meeting Abstract). (Eng.) Glowinski, I. B. (Univ. Michigan Medical Sch., Pharmacology, Ann Arbor, MI 48109) Radtke, H. E.; Weber, W. W. *Pharmacologist* 18(2): 231; 1976. (no refs.)

77-1260 **Repairable and Non-Repairable Lesions Induced in Rat Liver DNA by Carcinogenic Aromatic Amines** (Meeting Abstract). (Eng.) Kriek, E. (Chemical Carcinogenesis Div., Antoni van Leeuwenhoek-Huis, The Netherlands Cancer Inst., Amsterdam, The Netherlands) Festra, J. G. *Mutat Res* 46(2): 132-133; 1977. (3 refs.)

77-1261 **The Acute Effects of N-Hydroxy Acetylaminofluorene on Rat Liver Protein Synthesis** (Meeting Abstract). (Eng.) Moyer, G. H. (UCLA, Los Angeles, CA 90024) Austin, G. E. *Fed Proc* 36(3): 349; 1977. (no refs.)

77-1262 **Possible Role of DNA Replication in Chemical Carcinogenesis: An Investigation of the In Vivo Replication of Rat Liver DNA Arylated by the Hepatocarcinogen N-Hydroxy-2-Acetylaminofluorene** (Meeting Abstract). (Eng.) Zahner, A. J. (Temple Univ., Philadelphia, PA 19122) *Diss Abstr Int [B]* 37(12/Part 1): 6112-6113; 1977. (no refs.)

77-1263 **Activation of 2-Acetylaminofluorene and N-Hydroxy-2-Acetylaminofluorene into Mutagens by Nuclear Membrane from Mouse Liver** (Meeting Abstract). (Eng.) Reinhold, C. E. (NICHD, NIH, Bethesda, MD 20014) Thorgeirsson, S. S. *Pharmacologist* 18(2): 210; 1976. (no refs.)

77-1264 **Mutagenic Activation of 2-Acetylaminofluorene and N-Hydroxy-2-Acetylaminofluorene by Mouse Liver and Kidney Microsomes** (Meeting Abstract). (Eng.) Schut, H. A. (NIH, Bethesda, MD 20014) Thorgeirsson, S. S. *Fed Proc* 36(3): 999; 1977. (no refs.)

77-1265 **Carcinogen-induced Repair and Binding in the DNA of Chronic Lymphocytic Leukemic Lymphocytes**. (Eng.) Pero, R. W. (Nucleic Acid Biochemistry, Lund Univ., Wallenberg Lab., Fack 7031, 220 07 Lund, Sweden) Bryngelsson, C.; Brandt, L. *Cancer Lett* 2(6): 311-318; 1977.

The induction of DNA repair synthesis by chemical carcinogens was studied in lymphocytes from 16 normal individuals and 16 patients with chronic lymphocytic leukemia (CLL). The lymphocytes were exposed to 10 μ M N-acetoxy-2-acetylaminofluorene and DNA synthesis was determined by measuring the incorporation of ³H-thymidine. The lymphocytes from 15/16 CLL patients had lower values of induced repair synthesis than the lymphocytes from normal individuals. The incubation of lymphocytes with 5 μ M ³H-labeled 7,12-dimethylbenz(a)anthracene (DMBA) showed that CLL lymphocytes consistently bound less DMBA in their DNA's than the normal lymphocytes. The data suggest that CLL lymphocytes have lower levels of carcinogen-induced DNA repair than normal lymphocytes because there is less initial DNA damage to stimulate repair synthesis in CLL lymphocytes. (22 refs.)

- 77-1266 **DNA Repair and DNA Binding of Chemical Carcinogens as Indicators of the Carcinogen-sensitive Individual (Meeting Abstract).** (Eng.) Pero, R. W. (Wallenberg Lab., Univ. Lund, Lund, Sweden) *Hereditas* 84(1): 130-131; 1976. (no refs.)
- 77-1267 **Murine Erythroleukemia Cells: Induction to Erythroid Differentiation with Hexamethylene Bisacetamide (Meeting Abstract).** (Eng.) Reuben, R. C. (Columbia Univ., New York, NY 10032) Rifkind, R. A.; Marks, P. A. *Fed Proc* 36(3): 886; 1977. (no refs.)
- 77-1268 **Inhibition of Aflatoxin Biosynthesis by 2-Mercaptoethanol (Meeting Abstract).** (Eng.) Gupta, S. K. (Dept. Biochemistry, V. P. Chest Inst., Univ. Delhi, Delhi, India) Maggon, K. K. *Ind J Biochem Biophys* 14(1/Suppl): 54; 1977. (no refs.)
- 77-1269 **Inhibition of Aflatoxin Biosynthesis by Tolnaf-tate (Meeting Abstract).** (Eng.) Khan, S. N. (Dept. Biochemistry, Vallabhbhai Patel Chest Inst., Univ. Delhi, Delhi, India) Maggon, K. K. *Ind J Biochem Biophys* 14(1/Suppl): 36; 1977. (no refs.)
- 77-1270 **Genetics of Aflatoxin B₁ (AFB₁) Metabolism in Various Inbred Strains of Mice, Offsprings of Selected Matings and in Recombinant Inbred Sublines (Meeting Abstract).** (Eng.) Gurtoo, H. L. (Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY) Dahms, R.; Motycka, L.; Taylor, B. *Fed Proc* 36(3): 939; 1977. (no refs.)
- 77-1271 **Hepatic Uptake and Disposition of Aflatoxin B₁ (Meeting Abstract).** (Eng.) Unger, P. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS 39216) Mehendale, H. M.; Hayes, A. W. *Pharmacology* 18(2): 195; 1976. (no refs.)
- 77-1272 **Carcinogen-Protein Complexes in Liver Cytosol During Hepatocarcinogenesis by Aflatoxin B₁ (Meeting Abstract).** (Eng.) Mainigi, K. D. (The Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111) Sorof, S. *Fed Proc* 36(3): 349; 1977. (no refs.)
- 77-1273 **Effects of Subacute Aflatoxin B₁ Treatment on Hamster Liver Microsomal Mixed Function Oxidase Activity (Meeting Abstract).** (Eng.) Tucker, A. N. (Dept. Pharmacology, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA 23298) Tang, T.; Friedman, M. A.; Egle, J. L. *Fed Proc* 36(3): 940; 1977. (no refs.)
- 77-1274 **The Relationship Between Hepatic Glutathione Levels and the Formation of Aflatoxin B₁-DNA Adducts as Influenced by Dietary Protein Intake (Meeting Abstract).** (Eng.) Allen-Hoffman, B. L. (Cornell Univ., Ithaca, NY 14853) Campbell, T. C. *Fed Proc* 36(3): 1116; 1977. (2 refs.)
- 77-1275 **DNA Repair in Human Cells Treated with Activated Aflatoxin B₁ (Meeting Abstract).** (Eng.) Sarasin, A. (Dept. Biological Sciences, Stanford Univ., Stanford, CA 94305) Hanawalt, P. *Mutat Res* 46(2): 151; 1977. (7 refs.)
- 77-1276 **Moisture-Equilibrium Relative Humidity Relationships in Pistachio Nuts with Particular Regard to Control of Aflatoxin Formation.** (Eng.) Denizel, T. (A. U. Ziraat Fakultesi, Ziraat Mikrobiyolojisi Kursusu, Diskapi, Ankara, Turkey) Rolfe, E. J.; Jarvis, B. *J Sci Food Agric* 27(11): 1027-1034; 1976.
- Adsorption and desorption isotherms were examined both nanometrically and by wt equilibration for the Turkish pistachio kernel, shell, and hull. A good correlation was found between the calculated and experimentally determined adsorption isotherms for whole nuts. The nuts were imported in bulk from Turkey, and they were typical hand-selected dehulled nuts and mature nuts still in the hull. Metabolic moisture from the growth of *Aspergillus amstelodami* in sealed containers at 28 C increased the moisture-equilibrium relative humidity (ERH) from the initial 85% and allowed toxin production by *A. flavus*. Significant aflatoxin production occurred at 88% ERH, but competition was noted between *A. niger* and *A. flavus*. At an ERH of $\leq 86\%$, competitive growth of xerophilic strains of *A. amstelodami* prevented aflatoxin production and growth by *A. flavus*. The results demonstrate that nuts stored without hulls are less likely to suffer from aflatoxin contamination than nuts stored within the hull. They provide data on moisture sorption isotherms that can be used to ensure adequate drying and control of subsequent storage of the nuts. (14 refs.)
- 77-1277 **Effect of Rubratoxin B and Aflatoxin B₁ on ATPase Activities in the Mouse (Meeting Abstract).** (Eng.) Hayes, A. W. (Dept. Pharmacology and Tox-

cology, Univ. Mississippi Medical Center, Jackson, MS 39216) Desai, D.; Ho, I. K. *Pharmacologist* 18(2): 170; 1976. (no refs.)

77-1278 **The Effect of Aflatoxin on Chinese Hamster Cells in Culture (Meeting Abstract).** (Eng.) Kuśniak, R. (Inst. Systematic and Experimental Zoology, Polish Acad. Sciences, Cracow, Poland) *Mutat Res* 46(3): 227; 1977. (no refs.)

77-1279 **Comparative In Vitro Biochemical Effects of Patulin and Aflatoxin B₁ (Meeting Abstract).** (Eng.) Peters, E. L. (Div. Toxicology, FDA, Washington, DC 20204) Keys, J. E.; Friedman, L. *Fed Proc* 36(3): 397; 1977. (no refs.)

77-1280 **Isolation and Toxicity of Molds from Foods Stored in Homes.** (Eng.) Torrey, G. S. (Dept. Food Science, Univ. Wisconsin-Madison, Madison, WI 53706) Marth, E. H. *J Food Protection* 40(3): 187-190; 1977.

Molds collected from home-stored foods were partially identified, and their potential for mycotoxin production was assessed. Samples were taken from refrigerated and nonrefrigerated food and from refrigerator surfaces. *Penicillia* (49% of 155 isolates) and *aspergilli* (38%) were the predominant molds. Aflatoxin (9 isolates), kojic acid (3), ochratoxin A (3) penicillic acid (1), and patulin (1) were detected when culture extracts of isolates were screened for the presence of toxic mold metabolites. Six of the nine cultures that were aflatoxigenic were from nonrefrigerated food (3 from bakery goods, 2 from spices, and 1 from home-canned pumpkin), and three were from refrigerated samples (cheese, cottage cheese, and a cake of compressed yeast). A published study has indicated that *Aspergillus flavus* and other molds with known oncogenic properties for animals were found more frequently in dwellings, food, and wall surfaces associated with patients suffering from neoplastic diseases than in dwellings of control families not affected by these diseases. A more serious attitude, therefore, should be taken toward the presence of molds in home-stored foods. (22 refs.)

77-1281 **Investigations on Carcinogenic Effects of Penicillin Caseicolum and *P. Roqueforti* in Rats.** (Eng.) Frank, H. K. (Institut für Biologie der Bundesforschungsanstalt für Ernährung, Engesserstrasse 20, D-7500 Karlsruhe, W. Germany) Orth, R.; Ivankovic, S.; Kuhlmann, M.; Schmahl, D. *Experientia* 33(4): 515-516; 1977.

To determine the carcinogenic effects of *Penicillin caseicolum*

and *P. roqueforti* in rats, 800 Sprague-Dawley rats were fed commercial starters for camembert and blue-cheese. The feeding test continued over the whole life span of the rats. The rats showed no acute-toxic lesions during the treatment and wt development was in the normal range. Tumor incidence was not significantly higher in the commercial cheese-fed group than in the control group. The results indicate that a carcinogenic effect can be assigned neither to the starters used in German cheese technology, nor to their products. (5 refs.)

77-1282 **Stable Incorporation of Plasmid DNA into Higher Plant Cells: the Molecular Basis of Crown Gall Tumorigenesis.** (Eng.) Chilton, M. D. (Dept. Microbiology and Immunology, Univ. Washington, Seattle, WA 98195) Drummond, M. H.; Merlo, D. J.; Sciaky, D.; Montoya, A. L.; Gordon, M. P.; Nester, E. W. *Cell* 11(2): 263-271; 1977.

DNA hybridization studies were carried out, demonstrating that crown gall tumors are caused by the incorporation of part of a virulence plasmid carried by the inciting bacterium, *Agrobacterium tumefaciens*. The rate of reassociation of labeled plasmid DNA was slightly accelerated in the presence of tobacco crown gall tumor DNA but not to normal tobacco callus DNA; DNase treatment abolished the acceleration. To determine whether all plasmid sequences are represented in tumor DNA, the labeled plasmid DNA was separated into specific fragments after digestion with restriction endonuclease Sma I. Renaturation rates for DNA from bands 1, 2, 7, 8, 9, 12, and 14 were not affected by tumor DNA. DNA from band 3 showed a slight rate increase in the presence of tumor DNA. The band 3 doublet was separated by electrophoresis into bands 3a and 3b. Tumor DNA had little effect on the reassociation rate of the 3a band; band 3b DNA renatured rapidly in the presence of tumor DNA, its rate increase indicating that approx 18 copies of 40% of band 3b DNA sequences are present per diploid tumor cell. This amounts to 3.7×10^6 daltons of foreign genetic information and represents a contribution of 0.0011% to tumor DNA. The etiological similarities between this plant tumor and virus-induced animal tumors might warrant the use of the crown gall tumor system as a model of neoplastic transformation in animals. (40 refs.)

77-1283 **Radioimmunoassay for a Derivative of 4-Aminobiphenyl (Meeting Abstract).** (Eng.) Johnson, H. J. (Univ. Arkansas Medical Center, Little Rock, AR 72201) Cernosek, S. F.; Cernosek, R. M. *Fed Proc* 36(3): 867; 1977. (no refs.)

77-1284 **Identification of the N-Oxidized Metabolite of 4-Aminobiphenyl in Dog Urine (Meeting Ab-**

stract). (Eng.) Moreno, H. R. (Univ. Miami, Miami, FL 33152) Hearn, W. L.; Radomski, T. *Fed Proc* 36(3): 999; 1977. (no refs.)

77-1285 **Adult Rat Liver Epithelial Cells for Studies of Carcinogenic Activity of Saffrole (Meeting Abstract).** (Eng.) Janiaud, P. (Lab. Biochimie Medicale, UER de Medecine, 21033 Dijon, France) Padiou, P. *Mutat Res* 46(3): 221-222; 1977. (no refs.)

77-1286 **Studies of the Mechanism of Organotropy Shown by the Carcinogen Methylazoxymethanol Acetate (MAM) (Meeting Abstract).** (Eng.) Grab, D. J. (Sloan-Kettering Inst., New York, NY 10021) Zedeck, M. S. *Fed Proc* 36(3): 348; 1977. (no refs.)

77-1287 **Activation of γ -Glutamyl Transferase in Rat Liver by Disulfiram and Its Effect on the First Stage of Azo-Dye Induced Carcinogenesis (Meeting Abstract).** (Eng.) Fiala, S. (Cell Physiology Lab., VAC, Martinsburg, WV 25401) Fiala, A. E.; Keller, R. W. *Fed Proc* 36(3): 349; 1977. (no refs.)

77-1288 **Biliary Excretion of Metabolites of N,N-Dimethylaminoazobenzene (DAB) in the Rat (Meeting Abstract).** (Eng.) Levine, W. G. (Albert Einstein Coll. Medicine, Bronx, NY 10461) Finkelstein, T. *Fed Proc* 36(3): 1030; 1977. (no refs.)

77-1289 **Magnesium Concentration Changes in Blood and in "Target" Tissue During Carcinogenesis (Letter to Editor).** (Eng.) Anghileri, L. J. (Innere Klinik und Poliklinik, Tumorforschung, Universitäts-klinikum der GHS Essen, Hufelandstrasse 33, 4300 Essen 1, W. Germany) Heidebreder, M. *Eur J Cancer* 13(3): 291-292; 1977.

Data are presented on the mineral content of blood and liver tissue of Wistar rats fed a diet containing 0.06% 4-dimethylaminoazobenzene (DAB). Blood magnesium and phosphorus increased significantly during the development of DAB-induced liver tumors. In tumor-bearing animals, a 50% increase in blood magnesium was accompanied by a 30% decrease of this element in tumor tissue. No correlation was evident between high levels of calcium and sodium in tumor tissue and their concentrations in blood. (5 refs.)

77-1290 **Aryl and Heterocyclic Diazo Compounds as Potential Environmental Electrophiles.** (Eng.) Lower, G. M. (Div. Clinical Oncology, Univ. Wisconsin Medical Sch., Madison, WI 53706) Lanphear, S. P.; Johnson, B. M.; Bryan, G. T. *J Toxicol Environ Health* 2(5): 1095-1107; 1977.

4-Aminoimidazole-5-carboxamide (AIC), a component of human urine derived from the de novo purine biosynthetic pathway, was shown to undergo in vivo diazotization in female Sprague-Dawley rats following its sequential administration (1.95 mg of the hydrochloride salt of [2-¹⁴C] AIC) with sodium nitrite. The diazotization product, 4-diazoimidazole-5-carboxamide, underwent intramolecular cyclization to yield 2-azahypoxanthine, which was then revealed in the urine by mass spectrometry. 4-Diazoimidazole-5-carboxamide demonstrated dose-related mutagenicity in *Salmonella typhimurium* TA 100; it is a potent electrophilic reactant similar to the proposed ultimate carcinogenic forms of arylalkylnitrosamines and arylnitrosamides. It is suggested that, as a class, aryl and heterocyclic diazo compounds warrant further study as environmental electrophiles representing potential biological hazard. (40 refs.)

77-1291 **Purification and Characterization of Arylhydroxamic Acid Acyltransferase (Meeting Abstract).** (Eng.) Allaben, W. T. (NCTR, FDA, Jefferson, AR 72079) King, C. M. *Fed Proc* 36(3): 349; 1977. (no refs.)

77-1292 **Studies on the Intestinal Absorption of Bovine Xanthine Oxidase in Rats (Meeting Abstract).** (Eng.) Volp, R. F. (Sch. Pharmacology, Univ. Wisconsin, Madison, WI 53706) Lage, G. L. *Pharmacologist* 18(2): 158; 1976. (no refs.)

77-1293 **The Influence of the Mode of Administration of Mutagens on the Aberration Frequency of Mouse Bone Marrow and Ascites Tumour Cells (Meeting Abstract).** (Eng.) Wobus, A. M. (Zentralinstitut für Genetik und Kulturpflanzenforschung Gatersleben, E. Germany) Thieme, R.; Schoneich, J. *Mutat Res* 46(3): 242; 1977. (no refs.)

77-1294 **Synergism Between Mitomycin C and Caffeine in Normal Human Fibroblasts and Two Xeroderma Pigmentosum Cell Strains (Meeting Abstract).** (Eng.) Hartley-Asp, B. (Inst. Genetics, Univ. Lund, Sweden) *Mutat Res* 46(3): 42; 1977. (no refs.)

7-1295 **Effects of Phorbol Myristate Acetate and Related Derivatives on Chick Fibroblasts (Meeting Abstract).** (Eng.) Driedger, P. E. (Harvard Medical Sch., Boston, MA 02115) Blumberg, P. M. *Fed Proc* 36(3): 701; 1977. (no refs.)

7-1296 **Early Effects of Phorbol Esters on Membrane Transport (Meeting Abstract).** (Eng.) Moroney, J. V. (Roswell Park Memorial Inst., Buffalo, NY 14263) Wenner, C. E. *Fed Proc* 36(3): 693; 1977. (no refs.)

7-1297 **The Effect of the Co-Carcinogen TPA on Chemical Mutagenesis in Bacteria (Meeting Abstract).** (Eng.) Soper, C. J. (Pharmaceutics Dept., Sch. of Pharmacy and Pharmacology, Univ. Bath, Bath, England) Evans, F. J. *Mutat Res* 46(3): 238; 1977. (no refs.)

7-1298 **Unbalanced Ribosomal RNA Accumulation in Regenerative and "Preneoplastic" Epidermal Hyperplasia (Meeting Abstract).** (Eng.) Argyris, T. S. (Dept. of Pathology, Upstate Medical Center, Syracuse, NY 13210) *Fed Proc* 36(3): 1078; 1977. (no refs.)

7-1299 **Two-Stage Carcinogenesis with Rat Embryo Cells in Tissue Culture.** (Eng.) Lasne, C. (Institut de Recherches Scientifiques sur le Cancer, Laboratoire de Medecine Experimentale, C.N.R.S.-B.P. No 8, 94800, Villejuif, France) Gentil, A.; Chouroulinkov, I. *Br J Cancer* 35(6): 722-729; 1977.

The transformation of Wistar rat embryo fibroblasts in vitro was investigated using initiation with benzo(a)pyrene (BaP, 1 µg/ml), 7,12-dimethylbenz(a)anthracene (DMBA, 0.5 µg/ml), or benzo(e)pyrene (BeP, 1 µg/ml) and promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA, 0.01 µg/ml) or croton oil (0.01 µg/ml). The criteria for assessing in vitro transformation were the efficiency of cloning in liquid medium, abnormal cellular morphology, and the development of malignant tumors following sc inoculation into newborn rats. Cloning efficiency increased to a variable extent in the treated groups, remaining low in control cells. Transformation occurred in all cell groups but was accelerated in cells that were initiated and promoted. Initiation with DMBA or BaP and promotion with TPA or croton oil led to the earliest acquisition of malignancy. Correlations were found between the transformation of cells in vitro and the acquisition of malignant potential, and between the in vitro and in vivo carcinogenicity of the compounds; however, cloning efficiency was not a reliable indicator of in vitro transformation or of malignancy. In vitro transformation preceded the acquisition

of malignancy in all but two cases. A two-stage carcinogenesis model is proposed that may be useful for studying the processes of initiation and promotion in tissue culture. (26 refs.)

77-1300 **Determination and Identification of Polycyclic Aromatic Hydrocarbons in Smoked and Charcoal-Broiled Food Products by High Pressure Liquid Chromatography and Gas Chromatography.** (Eng.) Panalaks, T. (Food Res. Labs., Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada K1A 0L2) *J Environ Sci Health [B]* B11(4): 299-315; 1976.

High pressure liquid chromatography (HPLC), using both UV and fluorescence detectors, was employed to determine the content of polycyclic aromatic hydrocarbons (PAH) in 70 samples of smoked food products and in 6 charcoal broiled meats available in Canada. PAHs were detected in approx 70% of the samples tested. In some cases gas-liquid chromatography was used to confirm the findings. (19 refs.)

77-1301 **Control of Mutagenic Benzo(a)pyrene Metabolites by Epoxide Hydratase and Glutathione (Meeting Abstract).** (Eng.) Glatt, H. R. (Pharmakologisches Institut der Universitat Mainz, D-6500 Mainz, W. Germany) Bentley, P.; Oesch, F. *Experientia* 33(6): 792; 1977. (no refs.)

77-1302 **Receptors for Epidermal Growth Factor (EGF) and Fibroblast Growth Factor in Chemical Transformed Mouse Embryo 3T3 Cells (Meeting Abstract).** (Eng.) Yeh, Y. (Molecular Biology Lab., The Salk Inst., P. O. Box 1809, San Diego, CA 92112) Holley, R. W. *Fed Proc* 36(3): 711; 1977. (no refs.)

77-1303 **Benzpyrene-Induced Sister Chromatid Exchanges in Lymphocytes of Patients with Lung Cancer.** (Eng.) Schonwald, A. D. (Univ. Hamburg, Dept. Internal Medicine, Martinistrasse 52, D-2000 Hamburg 20, W. Germany) Bartram, C. R.; Rudiger, H. W. *Hum Genet* 36(3): 261-264; 1977.

The effect of benzpyrene on sister chromatid exchange was determined in phytohemagglutinin-stimulated lymphocytes of 18 patients with lung cancer and 11 controls without cancer or bronchopulmonary diseases. Patients and controls did not differ either with respect to the spontaneous rate of sister chromatid exchanges or in their response to the carcinogen. It is concluded that individual susceptibility to lung cancer cannot be detected by an individual lymphocyte response to benzpyrene at the chromosomal level. (16 refs.)

77-1304 Benzpyrene Metabolism and its DNA Binding in Pregnant and Pseudopregnant Rats (Meeting Abstract). (Eng.) Ling, T. H. (Dept. Pharmacology, Howard Univ. Coll. Medicine, Washington, DC 20059) Sperling, F.; West, W. L. *Pharmacologist* 18(2): 232; 1976. (no refs.)

77-1305 Metabolism of Benzo(a)pyrene and Benzo(a)pyrene-4,5-Oxide by the Isolated Perfused Rabbit Lung (Meeting Abstract). (Eng.) Smith, B. R. (NIEHS, NIH, Research Triangle Park, NC 27709) Bend, J. R. *Fed Proc* 36(3): 999; 1977. (no refs.)

77-1306 The Effects of Antioxidants on the Metabolism and Mutagenicity of Benzo(a)pyrene In Vitro. (Eng.) Rahimtula, A. D. (Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland, Canada A1C 5S7) Zachariah, P. K.; O'Brien, P. J. *Biochem J* 164(1): 473-475; 1977.

The effect of various antioxidants on the flavoprotein NADPH-cytochrome P-450 reductase, on benzo(a)pyrene (BP) hydroxylation and on the mutagenicity of BP metabolites in *Salmonella typhimurium* strain TA 98 was studied. The following antioxidants were tested: N,N,N',N'-tetramethyl-p-phenylenediamine dihydrochloride, butylated hydroxytoluene, butylated hydroxyanisole, nordihydroguaiaretic acid, propyl gallate, ethoxyquin, glutathione, ascorbate, and pyrogallol. All the antioxidants except glutathione inhibited BP hydroxylation in rat liver microsomal fractions; none had any effect on the flavoprotein. This indicates that the antioxidants do not inhibit BP hydroxylation via their effect on the flavoprotein; instead, they must do so by a more direct effect on cytochrome P-450. All of the compounds tested inhibited the mutagenicity of BP in strain TA 98 in the presence of microsomal fraction and NADPH, but they had no effect on the growth of TA in the absence of microsomal fraction. These findings suggest that the protective effect of these antioxidants in vivo may be due to their ability to inhibit the formation of carcinogenic metabolites from BP and other polycyclic hydrocarbons. (18 refs.)

77-1307 Flow Microfluorometric Analysis of Hydroxybenzo(a)pyrene in Single Cells and Sorting (Meeting Abstract). (Eng.) Cantrell, E. T. (Texas Coll. Osteopathic Medicine, North Texas State Univ., Denton, TX 76203) Tyrer, H.; Adams, A.; Dennis, R.; Busbee, D. L. *Pharmacologist* 18(2): 206; 1976. (no refs.)

77-1308 Genetic Differences in the Aromatic Hydrocarbon-Inducible N-Hydroxylation of N-Acetylarylamines in Mice (Meeting Abstract). (Eng.) Wirth,

P. J. (NICHD, NIH, Bethesda, MD 20014) Lambert, G. H.; Thorgeirsson, S. S. *Pharmacologist* 18(2): 158; 1976. (no refs.)

77-1309 Nuclear Aryl Hydrocarbon Hydroxylase (AHH) and Macromolecular Binding (Meeting Abstract). (Eng.) Bresnick, E. (Univ. Vermont Coll. Medicine, Burlington, VT 05401) Vaught, J. B.; Chuang, A. H. *Fed Proc* 36(3): 999; 1977. (no refs.)

77-1310 Activity of Intestinal Aryl Hydrocarbon Hydroxylase in Guinea Pigs Fed High Element Containing Sludge-Grown Cabbage (Meeting Abstract). (Eng.) Stoewsand, G. S. (Inst. Food Science, Cornell Univ., Geneva, NY 14456) Babish, J. G.; Lisk, D. J. *Fed Proc* 36(3): 1146; 1977. (1 ref.)

77-1311 Association of Increases in Single Electrophoretic Band with Aryl Hydrocarbon Hydroxylase Increased by Numerous Inducers in Cell Cultures (Meeting Abstract). (Eng.) Kano, I. (Developmental Pharmacology Branch, NICHD, NIH, Bethesda, MD 20014) Nebert, D. W. *Pharmacologist* 18(2): 210; 1976. (no refs.)

77-1312 Ascorbic Acid Deficiency (AA-DEF) and Phenobarbital (PB) Induction of Extrahepatic Metabolism of Drugs and Carcinogens (Meeting Abstract). (Eng.) Kuenzig, W. (Roche Res. Center, Nutley, NJ 07110) Tkaczewski, V.; Kamm, J. J.; Conney, A. H.; Burns, J. J. *Pharmacologist* 18(2): 154; 1976. (no refs.)

77-1313 Heterogeneity of Size and Function in Hepatocytes: Effects of 3-Methyl Cholanthrene (3-MC) and Phenobarbital (PB) (Meeting Abstract). (Eng.) Sweeney, G. D. (McMaster Univ. Medical Centre, Hamilton, Ontario, Canada L8S 4J9) *Fed Proc* 36(3): 960; 1977. (no refs.)

77-1314 Metyrapone Inhibition of Benzo[a]pyrene Hydroxylase in Hepatic Microsomes from Rats Treated with Phenobarbital or 3-Methylcholanthrene (Meeting Abstract). (Eng.) Enyeart, J. A. (Harrison Dept. Surgical Res., Medical Sch. Univ. Pennsylvania, Philadelphia, PA 19174) Cooper, D. Y.; Schleyer, H.; Rosenthal, O. *Fed Proc* 36(3): 961; 1977. (no refs.)

77-1315 Spectral Characterization of Purified Hepatic Cytochrome P-450 from 3-Methylcholanthrene-Treated and Untreated Rabbits (Meeting Abstract). (Eng.)

ailpot, R. M. (NIEHS, NIH, Research Triangle Park, NC 27709) Serabjit-Singh, C. J. *Fed Proc* 36(3): 990; 1977. (no refs.)

7-1316 Immunological Properties of Highly Purified Cytochrome P-450 from Aroclor 1254-Treated Rats (Meeting Abstract). (Eng.) Ryan, D. E. (Dept. Biochemistry and Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110) Thomas, P. E.; Levin, W. *Fed Proc* 36(3): 991; 1977. (no refs.)

7-1317 Purification of Liver Microsomal Cytochrome P-450 from Rats Treated with the Polychlorinated Biphenyl Aroclor 1254 (Meeting Abstract). (Eng.) Ryan, D. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NY 07710) Thomas, P. E.; Lu, A. Y.; West, S.; Levin, W. *Pharmacologist* 18(2): 241; 1977. (2 refs.)

7-1318 Amaranth Reductase, a Cytochrome P-450 Diaphorase Activity in Rat Liver Microsomes (Meeting Abstract). (Eng.) Fujita, S. (Albert Einstein Coll. of Medicine, Bronx, NY 10461) Peisach, J. *Pharmacologist* 18(2): 206; 1976. (no refs.)

7-1319 Sex Differences in Hepatic Microsomal Cytochrome P-450 in Spawning Trout (Meeting Abstract). (Eng.) Stegeman, J. J. (Woods Hole Oceanographic Inst., Woods Hole, MA 02543) *Fed Proc* 36(3): 941; 1977. (no refs.)

7-1320 Microsomal Cytochromes P-450: Separation, Purification, and Activities Toward Toxic Substrates (Meeting Abstract). (Eng.) Guengerich, F. P. (Vanderbilt Univ., Nashville, TN 37232) *Fed Proc* 36(3): 664; 1977. (no refs.)

7-1321 Stereospecificity of Rat Liver Cytochrome P-450 Monooxygenases and Epoxide Hydrase (Meeting Abstract). (Eng.) Thakker, D. R. (NIH, NIDDK, Bethesda, MD 20014) Lu, A. Y.; Levin, W. *Fed Proc* 36(3): 959; 1977. (no refs.)

77-1322 Reconstituted NADH-Dependent Benzo[a]pyrene Hydroxylase: Stimulation by NADPH-Cytochrome c Reductase (Meeting Abstract). (Eng.) West, S. B. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110) Ryan, D.; Levin, W.; Lu, A. Y. *Pharmacologist* 18(2): 241; 1977. (2 refs.)

77-1323 Liver Microsomal DT Diaphorase: Noninvolvement in Hydroxylation of Benzo(a)pyrene (Meeting Abstract). (Eng.) West, S. B. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110) Huang, M. T.; Lu, A. Y. *Fed Proc* 36(3): 959; 1977. (no refs.)

77-1324 Chronic Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in Rats (Meeting Abstract). (Eng.) Miller, J. P. (Univ. Wisconsin, Madison, WI 53706) Allen, J. R. *Fed Proc* 36(3): 396; 1977. (no refs.)

77-1325 Cytosolic Receptor for Ah Locus: Evidence for Regulatory Gene Dysfunction in Nonresponsive Cell Cultures Containing the Receptor (Meeting Abstract). (Eng.) Guenther, T. M. (Developmental Pharmacology Branch, NICHD, NIH, Bethesda, MD 20014) Nebert, D. W. *Fed Proc* 36(3): 648; 1977. (no refs.)

77-1326 In Vitro Activation of Monooxygenases in Human Liver by 7,8-Benzoflavone (Meeting Abstract). (Eng.) Buening, M. K. (Hoffman-La Roche Inc., Nutley, NJ 07110) Kapitulnik, J.; Poppers, P. J.; Fortner, J. G.; Conney, A. H. *Fed Proc* 36(3): 940; 1977. (no refs.)

77-1327 Induction of Hepatic Monooxygenase Activity in Chickens by 3-Methylcholanthrene (Meeting Abstract). (Eng.) Buynitzky, S. J. (Univ. Georgia, Athens, GA, 30602) Ragland, W. L.; Wade, A. E. *Fed Proc* 36(3): 941; 1977. (no refs.)

77-1328 Temporal Relationship of In Vivo Pancreatic and Hepatic Metabolism of 3-Methylcholanthrene (Meeting Abstract). (Eng.) Black, O. (V.A. Hosp. (FHD), and Medical Coll. Georgia, Augusta, GA 30909) *Fed Proc* 36(3): 594; 1977. (no refs.)

- 77-1329 **Electron Microscopic Study of the Development of Experimentally Induced Cerebral Metastasis (Meeting Abstract).** (Eng.) Ballinger, W. E. (Univ. Florida, Coll. Medicine, Gainesville, FL 32610) Schimpff, R. D. *Fed Proc* 36(3): 1086; 1977. (no refs.)
- 77-1330 **A Carcinogen Induced "Protein-X Like" Substance in Mammalian Cells (Meeting Abstract).** (Eng.) Hart, R. W. (Radiologic and Molecular Res. Div., The Ohio State Univ. Hosp., N212 Columbus, OH 43210) McCloskey, J. A.; Davis, M. T. *Mutat Res* 46(2): 126; 1977. (4 refs.)
- 77-1331 **Inducibility of UDP-Glucuronyltransferase (GT) by 3-Methylcholanthrene (3MC) in Mouse Inbred Strains and Recombinant Inbred Sublines (Meeting Abstract).** (Eng.) Gessner, T. (Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY 14263) Gurtoo, H. L.; Taylor, B. *Pharmacologist* 18(2): 232; 1977. (1 ref.)
- 77-1332 **Dietary Protein, Mixed Function Oxidase Activity, and Mammary Carcinogenesis in Rats (Meeting Abstract).** (Eng.) Clinton, S. K. (Univ. Illinois, Urbana, IL 61801) Truex, C. R.; Visek, W. J. *Fed Proc* 36(3): 1163; 1977. (no refs.)
- 77-1333 **Effect of Antioxidant in Diets Containing Different Types and Amounts of Fat on Mammary Tumor Incidence Induced by a Single Dose of 7,12-Dimethylbenzanthracene (Meeting Abstract).** (Eng.) King, M. M. (Oklahoma Medical Res. Foundation, Oklahoma City, OK 73104) Bailey, D. M.; Gibson, D. D.; Pitha, J. V.; McCay, P. B. *Fed Proc* 36(3): 1148; 1977. (no refs.)
- 77-1334 **Quantitative Assessment of Epithelial Changes in Heterotopic Tracheal Transplants as a Result of Brief Carcinogen Exposure (Meeting Abstract).** (Eng.) Topping, D. C. (ORNL, Oak Ridge, TN 37830) Griesemer, R. A.; Nettesheim, P. *Fed Proc* 36(3): 1087; 1977. (no refs.)
- 77-1335 **Metabolism of 7,12-Dimethylbenz(a)anthracene in Mouse Skin Homogenates Analyzed with High-pressure Liquid Chromatography.** (Eng.) Digiovanni, J. (Dept. Pharmacology, Sch. Medicine SJ-30, Univ. Washington, Seattle, WA 98195) Slaga, T. J.; Berry, D. L.; Juchau, M. R. *Drug Metab Dispos* 5(3): 295-301; 1977.
- The metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) in epidermal homogenates from methylcholanthrene-pretreated female CD-1 mice was analyzed with high-pressure liquid chromatography. Without pretreatment, metabolism was undetectable. Specific activities in epidermal homogenates from pretreated mice were found to be approx 100 to 1,000 times lower than those observed in comparable incubations containing hepatic microsomes from MC-pretreated rats. The major metabolite formed was 7-hydroxymethyl-12-methylbenz(a)anthracene; other hydroxymethyl metabolites were also present in detectable quantities. The K-region diol was not measurably present. While 7,8-benzoflavone, 5,6-benzoflavone, and 17- β -estradiol were found to be potent inhibitors of the metabolic transformation of DMBA by epidermal homogenates in vitro, butylated hydroxytoluene and 1,1,1-trichloro-2,3-propene oxide had little effect on or enhanced metabolite formation from DMBA in vitro. (19 refs.)
- 77-1336 **Metabolism of 7,12-Dimethylbenz(a)anthracene by Normal and Regenerating Rat Livers.** (Eng.) Tomsak, R. L. (Inst. Pathology, Case Western Reserve Univ 2085 Adelbert Road, Cleveland, OH 44106) Cook, R. T. *J Cancer* 35(6): 713-721; 1977.
- The in vitro metabolism of [14 C]7,12-dimethylbenz(a)anthracene (DMBA, 5.46 mCi/millimole) by postmitochondrial supernates and microsomes from intact and regenerating Sprague-Dawley rat liver was studied. Both cell fractions from regenerating livers at 48, 72, and 96 h after partial hepatectomy metabolized less [14 C]DMBA than similar fractions from intact livers. Prior in vivo treatment with DMBA (25 mg/kg, ip) enhanced metabolism by the cell fractions from both groups, but specific activities of cell fractions from regenerating livers were always 60% or less of those from intact livers. Thin-layer chromatography of metabolites formed in incubations with either cell fraction revealed no distinct differences between ether- or water-soluble products of similar fractions from intact and regenerating livers. However, highly reproducible differences were observed between chromatograms of water-soluble metabolites formed by microsomes and postmitochondrial supernates in both intact and regenerating livers. The results suggest large differences in the metabolic capacity of intact and regenerating livers when expressed on a whole liver basis; however, additional factors may contribute to the increased retention of DMBA by regenerating livers. (39 refs.)
- 77-1337 **Apparent Resistance of the Integument of the Invertebrate *Lehmannia poirieri* to Production of Papillary Tumors by a Known Chemical Carcinogen.**

ng.) Arcadi, J. A. (13203 E. Hadley St., Whittier, CA 90601) *J Surg Oncol* 9(1): 87-91; 1977.

The failure of 7,12-dimethylbenz(a)anthracene (DMBA) to induce papillary skin tumors in the land invertebrate *Lehmnia poirieri* was studied. The slugs had their dorsolateral integument painted with a saturated soln of DMBA dissolved in dimethyl sulfoxide daily and/or biweekly for up to 6 mo. Another group was treated with a 20% soln of the same chemicals. No gross papillomatous tumors were found in any of the slugs. Hematoxylin- and eosin-stained sections of the integument revealed slight pleomorphism and increased basophilia, but were similar to those noted in regenerating slug epithelium. No mitoses were observed. Electron microscope tissue studies demonstrated a slight change in the nucleus and some irregularity of the microvilli. The nuclear membrane was irregular and the nucleus seemed somewhat distorted. The microvilli showed some increased density on their tip, and an occasional giant microvillus was found. The land slug may be, in its integument, an innate and undefined resistance to vertebrate carcinogenic agents. (7 refs.)

1338 **The Effect of Crocetin on Skin Papillomas and Rous Sarcoma.** (Eng.) Gainer, J. L. (Thornton Hall, Univ. Virginia, Charlottesville, VA 22901) Wallis, D. Jones, J. R. *Oncology* 33(5/6): 222-224; 1976.

The effect of a carotenoid compound, crocetin (CR), on papillomas in Swiss-Webster mice and Rous sarcomas in white Leghorn chicks was investigated. The mice were treated with 7,12-dimethylbenz(a)anthracene on days 1 and 15 of the test period: 0.2 ml of a 0.8-mg/ml soln in acetone was applied to a 4-cm² area of skin on the backs of the mice. The mice developed papillomas that were approx 1 mm in diameter. When 600 µg/kg/day of CR was administered ip, the number of papillomas was reduced significantly (p < 0.05). Applying CR directly to the affected area (600 µg/kg/day) reduced the numbers of skin tumors even more. In experiments involving Rous sarcoma, the initial injectate into the wing web was 0.1 ml of a 10⁻³ dilution of the original tissue of 4-day-old chicks. The amount of CR injected was 30 µg/chick per day for the lifetime of the chick or a daily dose of 600 µg/kg im. CR resulted in an ILS of approx 50%. In another experiment, a 10⁻³ dilution of the original tissue was injected into the wing web of 5-day-old chicks. One chick was injected with 50 µg/day of sodium CR for 1 wk at a dosage of 2,000 µg/kg. CR increased the latent period approx 10%. The results indicate that CR decreased the number of tumors and delayed their onset. (13 refs.)

1339 **In Vivo and In Vitro Effects of Dimethylbenz(a)anthracene on Nuclear Uptake of Estrogen-Receptor Complex in Rat Uterus.** (Eng.) Ianicello, C. M. (Dept. Biology, Univ. Windsor, Windsor, Ontario N9B 3P4, Canada) Okey, A. B. *Oncology* 33(5/6): 225-228; 1976.

The influence of 7,12-dimethylbenz(a)anthracene (DMBA) on the nuclear uptake of the estrogen-receptor complex in vitro and in vivo was studied. When immature Sprague-Dawley rats were inoculated sc with 0.05 µg ³H-estradiol-17β (E2) 24 hr after DMBA (20 mg po), DMBA decreased the uterine nuclear uptake of the estrogen-receptor complex. DMBA pretreatment in vivo significantly decreased the amount of ³H-E2 bound in the uterine cytosol and nuclei. The total tritium content of the cytosol or nuclei was not affected by DMBA. The uptake and binding of ³H-E2 in the cytosol and nuclei of whole uteri were not altered by the presence of 10 µM DMBA in the medium. DMBA also did not affect the uptake of preformed ³H-E2 receptor complex into purified uterine nuclei. Very little ³H-E2 was bound in the nucleus when the cytosol was charged with ³H-E2 at 4°C and held at that temperature during incubation with purified nuclei. DMBA may act in vivo by stimulating the hepatic degradation of injected E2 so that a less active form of the steroid reaches target tissues. In vitro, DMBA does not act by reducing estrogen-receptor transformation or transport into the nuclei. (17 refs.)

77-1340 **Enhanced Growth of Carcinogen-induced Mammary Tumors in Rats by Sulpiride.** (Eng.) Pass, K. A. (Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI 48824) Meites, J. *IRCS Med Sci: Cancer* 5(5): 241; 1977.

The effects of Sulpiride on the growth of carcinogen-induced mammary tumors in rats were determined. Female Sprague-Dawley rats were injected with 5 mg 7,12-dimethylbenz(a)anthracene (DMBA) iv and, approx 2 mo later, treated with Sulpiride. The animals received 0.05% or 0.025% Sulpiride via their drinking water or 10 mg Sulpiride injected sc. Controls were given distilled water. The administration of Sulpiride by either route caused a pronounced increase in the total number of new tumors, tumor growth, and the average number of new tumors per rat. The results demonstrate that Sulpiride can stimulate the growth of DMBA-induced mammary tumors in rats. The increased growth is believed to be the result of an increased secretion of prolactin. (4 refs.)

77-1341 **Investigations on the Mechanism of Hydrocarbon-Nitrosamine Syncarcinogenesis (Meeting Abstract).** (Eng.) Davies, D. L. (USPHS Res. Lab., Tulane Medical Center, New Orleans, LA 70118) Bryant, G. M.; Arcos, J. C.; Argus, M. F. *Pharmacologist* 18(2): 158; 1976. (no refs.)

77-1342 **Evidence for Dimethylnitrosamine-Demethylase Isoenzymes (Meeting Abstract).** (Eng.) Arcos, J. C. (USPHS Res. Lab., Tulane Medical Center, New Orleans, LA 70118) Davies, D. L.; Brown, C. E.; Argus, M. F. *Pharmacologist* 18(2): 211; 1976. (no refs.)

77-1343 Microsome-Mediated Mutagenesis of a Chinese Hamster Cell Line by Nitrosamines (Meeting Abstract). (Eng.) Kuroki, T. (International Agency for Res. on Cancer, Lyon, France) Drevon, C.; Montesano, R. *Mutat Res* 46(3): 205-206; 1977. (no refs.)

77-1344 Pre-Cancerous Transformation in Rat Liver by Diethylnitrosamine in Relation to the Repair of Alkylated Site in DNA (Meeting Abstract). (Eng.) Scherer, E. (Chemical Carcinogenesis Division, Antoni van Leeuwenhoek-Huis, The Netherlands Cancer Inst., Amsterdam, The Netherlands) *Mutat Res* 46(2): 153-154; 1977. (no refs.)

77-1345 The Effect of a Protein-Free Diet, A Sugar Diet and of Carbon Tetrachloride Administration on the Toxicity and Rate of Metabolism of Dimethylnitrosamine in Different Rat Strains. (Eng.) Waynforth, H. B. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London W1P 7PN, England) Parkin, R.; Stoddart, D. *J. Br J Exp Pathol* 58(2): 225-229; 1977.

Preconditioning on a protein-free and/or a sugar diet was shown to raise the LD₅₀ for dimethylnitrosamine (DMN) in a Porton and a hooded rat strain, but not appreciably in the Wistar, BDIX and CFY rat strains. Pretreatment with carbon tetrachloride (CCl₄) (2.5 ml/kg) did not alter significantly the toxicity of DMN in the Wistar strain. DMN (40 mg/kg body wt) metabolism was slowed significantly, the rates for the different strains being quantitatively similar. It is concluded that the toxicity of DMN is not necessarily related to its rate of metabolism and that the effect of diet or CCl₄ treatment on DMN toxicity is dependent on the strain of rat used. (16 refs.)

77-1346 In Vitro and In Vivo Effects of Dimethylnitrosamine on Mouse Liver Mitochondrial Function. (Eng.) Friedman, M. A. (Dept. Pharmacology, Medical Coll. Virginia, Health Sciences Div., Virginia Commonwealth Univ., Richmond, VA 23298) Watt, K. M.; Higgins, E. S. *Proc Soc Exp Biol Med* 154(4): 530-533; 1977.

The in vivo and in vitro effects of dimethylnitrosamine (DMN) on the metabolic activity of murine liver mitochondria were studied. Oxygen consumption by mitochondria was measured polarographically in the presence of ADP (State 3) and after the exhaustion of ADP (State 4) using succinate or glutamate as substrates. DMN in concentrations $\geq 37.8 \mu\text{M}$ significantly decreased State 3 glutamate oxidation. State 4 glutamate oxidation was inhibited significantly only at DMN concentrations of 75, 151, and 226 μM . The respiratory control ratio (RCR, the ratio of State 3 to State 4 oxygen utilization, which is indicative of the tightness

of coupling of the oxidative phosphorylation and electron transport systems) was decreased corresponding to the decrease in State 3 oxidation. Similar results were obtained using succinate as substrate. In mitochondria from mice treated with DMN (25 mg/kg ip), State 3 oxygen consumption was decreased, and the RCR was significantly different from control with either substrate. As in the in vitro studies, glutamate oxidation was more sensitive than succinate to DMN. These results indicate that DMN inhibits oxidative phosphorylation both in vivo and in vitro. (13 refs.)

77-1347 Enhancement of Hepatic and Renal Tumorigenesis in Thyroidectomized NZR/Gd Rat Treated with Dimethylnitrosamine. (Eng.) Noronha, R. F. (Dept. Surgery, Saint Louis Univ. Medical Sch., Saint Louis MO) Goodall, C. M. *J Surg Oncol* 8(6): 539-550; 1976.

Endocrine modulation of dimethylnitrosamine (DMN) carcinogenesis was investigated in male and female NZR/Gd rats preconditioned by starving for 48 hr and then inoculated ip once with 20 mg DMN/Kg. Ninety-seven rats were treated with DMN (45 intact and 52 thyroidectomized 45 days before DMN) and 149 animals were untreated (controls). Only 3/2 thyroidectomized female rats died within 48 hr of DMN treatment; thereafter, the survival of intact and thyroidectomized rats was indistinguishable. There was no sex difference in survival times of either DMN-treated or control rats. A sex difference in lung tumor incidence (male 70%, female 16%) was significant, and thyroidectomy decreased the sex differential (to 54% and 39%, respectively). Renal carcinomas demonstrated more signs of malignancy in thyroidectomized rats. Thyroidectomy increased DMN carcinogenesis. Intact rats developed kidney tumors. Kidney tumors were nearly all renal tubular adenomas and carcinomas, but in addition, there were kidney tumors of the mesenchymal histologic pattern. DMN-treated rats also developed hepatic endothelial cell tumors, alveolar lung tumors, and a significant number of nasal cavity tumors. The elevated incidence of kidney and liver tumors may be due to the altered metabolism of DMN in the tissues of thyroidectomized rats (49 refs.)

77-1348 Studies In Vivo of the Damage, Repair and Replication of Rat Liver DNA Alkylated by the Hepatocarcinogen, Dimethylnitrosamine and the Non-Hepatocarcinogen, Methylmethanesulfonate (Meeting Abstract). (Eng.) Abanobi, S. E. *Diss Abstr Int [B]* 37(12/Part 1): 6083-6084; 1977. (no refs.)

77-1349 Alteration in Pattern of DNA Synthesis in Pancreas Organ Culture Induced by Dimethylnitrosamine (DMN) (Meeting Abstract). (Eng.) Parsa, I

UNY, Downstate Medical Center, Brooklyn, NY 11203)
Proc 36(3): 348; 1977. (no refs.)

77-1350 **The Action of Pancreatic Carcinogens on the Hypertrophied Pancreas of the Rat (Meeting Abstract).** (Eng.) Morgan, R. G. (Dept. Therapeutics, Univ. Dundee, Dundee, Scotland) Hopwood, D.; Iwatsuk, N.; Levin, D.; Petersen, O. H.; Ueda, N.; Wormsley, K. G. *Scand Gastroenterol [Suppl]* 11(41): 67; 1976. (no refs.)

77-1351 **Effects of Sex Hormones on Oncogenesis in Rat Urinary Bladder by N-butyl-N-(4-hydroxybutyl)-nitrosamine.** (Eng.) Kono, N. (Dept. Urology, Tokyo Electric Power Hosp., 9-2, Shinanomachi, Shinjuku-ku, Tokyo, Japan) Tanahashi, T.; Suzawa, N.; Azuma, C. *Int Clin Pharmacol Biopharm* 15(3): 101-105; 1977.

The effects of testosterone propionate, estradiol, and estriol on the oncogenesis of bladder tumors induced by N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) were studied in maleistar-Imamichi rats. Six of 25 rats treated with BBN alone had bladder tumors, and two others showed hyperplasia. In the testosterone propionate group, nine developed tumors and two showed hyperplasia. In the estradiol group, two had tumors and 5 developed hyperplasia. In the estriol group, two showed bladder tumors and 3 had hyperplasia. External sex hormones can influence the experimental oncogenesis of bladder tumors in rats. (11 refs.)

77-1352 **Characterization of Human Cells Transformed In Vitro by N-Methyl-N'-nitro-N-nitrosoguanidine.** (Eng.) Rhim, J. S. (Microbiological Associates, Inc., Bethesda, MD 20014) Putman, D. L.; Arnstein, H.; Huebner, R. J.; McAllister, R. M. *Int J Cancer* 19(4): 55-510; 1977.

N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-treated and untreated human osteosarcoma (HOS) cultures were characterized in detail and compared to nonproducer KHOS cells transformed by Kirsten murine sarcoma virus (KiMSV). Hamsters inoculated with KHOS cells and MNNG-treated (0.1 µg/ml) HOS clonal lines developed tumors within a week. The tumors were rapidly growing, undifferentiated sarcomas. Hamsters inoculated with untreated cultures and MNNG-treated (0.1 µg/ml) cells failed to develop tumors within 2 wk. Nude mice given HOS cells treated with 0.1 µg/ml MNNG developed small, persistent nodules classified as osteosarcomas. Tumors failed to develop in dimethyl sulfoxide (DMSO)-treated controls. When transplanted into athymic antitoxin (ATS)-treated hamsters, the cells transformed by 0.01 µg/ml MNNG and KiMSV produced tumors, but those transformed by 0.01 µg/ml MNNG did not. Control HOS cells failed to grow in the aggregate form, but

they formed colonies in soft agar. These cells also formed smaller cell aggregates than those formed by MNNG- and KiMSV-transformed cells. The size of cell aggregates and the degree of cell proliferation correlated well with tumorigenicity in nude mice. (23 refs.)

77-1353 **Functional Perturbation in tRNA Induced by Chemical Carcinogen (Meeting Abstract).** (Eng.) Bagewadikar, R. S. (Biochemistry and Food Technology Div., Bhabha Atomic Res. Centre, Bombay, India) Bhattacharya, R. K. *Ind J Biochem Biophys* 14(1/Suppl): 41; 1977. (no refs.)

77-1354 **Temperal Aspects of Single-Strand Breaks and Their Repair After Treatment with the Carcinogen, N-Methyl-N-Nitrosoguanidine (Meeting Abstract).** (Eng.) Nikaido, O. (Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, England) Fox, B. W. *Mutat Res* 49(2): 144-145; 1977. (no refs.)

77-1355 **Induction of Malignant Skin Tumors in Mice by Topical Application of Ethylnitrosourea.** (Eng.) Pelfrene, A. F. (Dept. Safety Assessment, Searle Labs., Box 5110, Chicago, IL) *Experientia* 33(4): 520-521; 1977.

The repeated application of 1-ethyl-1-nitrosourea directly to the skin of 52 Swiss-Webster mice induced malignant skin tumors. A total of 34 skin tumors were obtained from the treated group. There were 28 invasive squamous cell carcinomas, 4 papillomas, and 1 keratoacanthoma. No skin tumors developed in the untreated control group. Other tumors induced included lymphomas and lung adenomas. (4 refs.)

77-1356 **The Role of the Subependymal Plate in the Origin of Gliomas Induced by Ethylnitrosourea in the Rat Brain.** (Eng.) Lantos, P. L. (Dept. Neurological Studies and Bland-Sutton Inst. Pathology, Middlesex Hosp. Medical Sch., London, W1P 8AA England) *Experientia* 33(4): 521-522; 1977.

Studies of the fine structure of early cell proliferations induced transplacentally by ethylnitrosourea (ENU) in the rat brain showed that the constituent cells were indistinguishable from subependymal plate cells. Common characteristics were high nuclear-cytoplasmic ratio, scarcity of cell organelles and dominance of free over membrane-bound ribosomes. The results indicate that most, if not all, gliomas induced by ENU originate from the subependymal plate. (11 refs.)

77-1357 Reduced Elimination of 06-Alkylguanine from the DNA of UV Repair Deficient Cells After Treatment with Alkylating Carcinogens (Meeting Abstract). (Eng.) Goth-Goldstein, R. (Donner Lab., Univ. California, Berkeley, CA 94720) *Radiat Res* 70(3): 685; 1977. (no refs.)

77-1358 Brain Tumor Induction by Methylnitrosourea. Influence of the Circadian Rhythm on Tumour Induction by Nitrosourea. (Eng.) Schreiber, D. (Martin-Luther-University, Inst. of Pathology, 402 Halle/Saale, Leninallee 14, E. Germany) Wessel, H.; Musil, A. *Neuropatol Pol* 15(1): 137-144; 1977.

Repeated ip injections of methylnitrosourea (MNU) 20 mg/kg/mo, max total dose 200 mg/kg yielded CNS and/or peripheral nervous system (PNS) tumors in 70-80% of rats. The results are contrary to a previous report that MNU given ip did not cause tumors of the nervous system. Besides tumors of the nervous system there were several extraneural neoplasms, including heart neoplasms. Tumors developed in 72% of 57 BD IX rats given MNU during their activity peak, and in 79% of hooded rats not intentionally scheduled. Because of the strain difference, conclusions based on the different incidence rates were not drawn. (18 refs.)

77-1359 Effect of BNU Treatment on Leukaemogenesis in Lethally Irradiated AKR Mice Restored with Bone-Marrow and Spleen Cells. (Eng.) Shisa, H. (Dept. Pathology, Saitama Cancer Center Res. Inst., Ina-Machi, Kita-Adachi-Gun, Saitama-Ken 362, Japan) Legrand, E.; Daculsi, R. *Int J Cancer* 19(4): 531-537; 1977.

The leukemogenic effect of N-butyl-N-nitrosourea (BNU) was studied in normal and thymectomized AKR mice that were lethally irradiated and restored with either bone-marrow (BM) or spleen cells. The administration of BNU to nonthymectomized mice restored with BM increased the percentage of spontaneous thymic lymphosarcomas (TLS) significantly and reduced survival from 265 to 205 days. The same response was observed after restoration with spleen cells. The admixture of thymic cells to BM or spleen cells enhanced thymic leukemogenesis: survival times were reduced from 205 to 187 days and from 198 to 166 days for the BM- and spleen-treated mice, respectively. All the leukemias, whether TLS or extrathymic (ETL), developed from the donor BM or spleen cells and never from the injected thymic cells. The majority of the TLS that occurred after BNU treatment in BM-restored mice were θ -negative, whereas most of the TLS that occurred in the controls and in the spleen cell-restored animals were θ -positive. The addition of thymic cells to the restorative inoculum suppressed θ -negative TLS in BM-restored mice. All ETL tested were negative for θ antigen. In thymectomized mice, the percentages of ETL and the mean survival times were not significant-

ly different in the groups restored by BM or spleen cells and not treated with BNU. BNU did not modify the percentage of leukemia in either the BM- or spleen cell-restored mice. The percentage of leukemias in spleen-restored BNU-treated mice was significantly higher than that of BM-restored BNU-treated mice. Most ETL had no detectable θ antigen. No cell bearing B markers were found in either the thymectomized or nonthymectomized mice. The results indicate that a negative T precursor could be involved in extrathymic leukemogenesis; however, a B precursor cannot be ruled out (16 refs.)

77-1360 Mutagenicity Testing in *Drosophila*; Comparison of Methods and Screening of Environmental Chemicals (Meeting Abstract). (Eng.) Blijleven, W. G. (Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratory, State Univ. Leiden, Leiden, The Netherlands) Kortseus, M. J.; Kramers, P. G. *Mutat Res* 46(3): 212; 1977. (no refs.)

77-1361 Comparative Mutagenicity Studies in Three Different Test Systems with the Nitrosourea CNU-Ethanol and BCNU (Meeting Abstract). (Eng.) Knaap, A. G. (Dept. Radiation Genetics and Chemical Mutagenesis, Univ. Leiden, The Netherlands) Kortseus, M. J.; Tate, A. D. *Mutat Res* 46(3): 225-226; 1977. (no refs.)

77-1362 Mutagenic Activity of Nitrite-treated Food. Human Stomach Cancer May Be Related to Dietary Factors. (Eng.) Marquardt, H. (Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY 10595) Rufino, F.; Weisburger, J. H. *Science* 196(4293): 1000-1001; 1977.

Extracts of beef, hot dogs, and Japanese raw fish were tested for mutagenic activity using the *Salmonella typhimurium* test. Extracts were prepared by subjecting these foods to nitrosation under simulated gastric conditions. The fish extract was highly mutagenic, but the homogenates of beef and hot dogs failed to show mutagenic activity. Addition to the fish extract of 28,000 ppm ascorbic acid, an amount equivalent to twice the molarity of nitrite used, completely prevented the formation of the mutagenic principle. The mutagenic activity found in nitrosated fish may be relevant to the etiology of human gastric cancer. Vitamin C and food rich in this nutrient may be useful in the prevention of gastric cancer (11 refs.)

77-1363 Mutagenicity of Nitrovin--A Nitrofurantoin Additive. (Eng.) Joner, P. K. (Dept. Food Hygiene, Coll. Veterinary Medicine, Oslo, Norway) Dahle, E. K.; Aune, T.; Dybing, E. *Mutat Res* 38(3-4): 313-318; 1977.

Nitrovin, a nitrofuran feed additive, was shown to be directly mutagenic in *Salmonella typhimurium* TA 98 and TA 100 between 0.1 and 2.5 μg per plate (0.09-2.3 μM). After addition of a rat-liver homogenate, there were considerably fewer histidine revertants per plate than without enzyme at the lower nitrovin concentrations. Nitrovin inhibited growth of the same bacteria in suspension cultures at concentrations above 0.09 μM . Because of its demonstrated cytotoxicity, nitrovin should be further evaluated for possible deleterious effects on mammalian cells and other bacteria. (14 refs.)

77-1364 A Comparison of Proline and Putrescine as Precursors of N-Nitrosopyrrolidine in Nitrite-Treated Pork Systems. (Eng.) Gray, J. I. (Dept. Food Science, Univ. Guelph, Guelph, Ontario, Canada N1G 2W1) Collins, M. E. *J Food Sci* 42(4): 1034-1037; 1977.

Proline and putrescine increased the levels of N-nitrosopyrrolidine (N-pyr) formed in model and pork systems containing 150 and 1,000 ppb sodium nitrite. Given the concentrations of proline and putrescine used in the study, the former was the more probable precursor of N-pyr in bacon. The distillate (condensate) collected on heating nitrite-treated pork samples in a heating flask was examined for its N-pyr content. Approx 27%-49% of the total N-pyr was volatilized during the cooking process. (24 refs.)

77-1365 Clastogenic Activity of 1,4-Dinitrosopiperazine in Ehrlich Ascites Tumor and Bone Marrow Cells of Mice (Meeting Abstract). (Eng.) Jakel, H. P. (Zentralinstitut für Genetik und Kulturpflanzenforschung der DDR, 4325 Gatersleben, E. Germany) Thieme, R.; Ziebarth, D.; Schoneich, J. *Mutat Res* 46(3): 220-221; 1977. (no refs.)

77-1366 Nitrosative Toxication of Drugs by Salivary Nitrite (Meeting Abstract). (Eng.) Rao, G. S. (Res. Inst., American Dental Assoc., Chicago, IL 60611) Drumley, J. O. *Fed Proc* 36(3): 412; 1977. (no refs.)

77-1367 Nitroso Group Exchange as a Way of Activation of Nitrosamines by Bacteria. (Eng.) Mandel, M. (Dept. Biochemistry and Biophysics, Univ. Hawaii at Manoa, Sch. Medicine, Honolulu, HI 96822) Ichinotsubo, D.; Mowbray, H. *Nature* 267(5608): 248-249; 1977.

The effect of 2-acetylaminofluorene (AAF) and/or dimethylnitrosamine (DMN) on the growth of *Escherichia coli* strain B1157 cells was studied. The DNA of these cells was radiolabeled, and the cells were exposed to AAF, DMN, or a mixture of both. The cells were then lysed on top of an

alkaline sucrose gradient and sedimented. The gradients showed that AAF + DMN produced alkali-labile lesions in the DNA, but AAF and DMN alone had no effect. AAF and DMN without microsomal activator had a negligible effect in producing revertants in the *his* - *Salmonella typhimurium* tester strain, but in the presence of sonicated bacterial extracts from AB1157 or *E. coli* strain JC5519, AAF + DMN became mutagenic in the standard Ames assay. When the AAF concentration was kept constant and the DMN concentration was varied in the presence of a JC5519 extract, the number of revertants rose with DMN concentration and then decreased with higher DMN concentrations. The results showed that a nitroso group exchange reaction in which the nitroso group was transferred from the nitrosamines to the amide moiety of AAF occurred. This reaction is being studied as a possible cause of colorectal cancer. (8 refs.)

77-1368 In Vitro AFP Synthesis by Monkey Hepatoma (Meeting Abstract). (Eng.) Princlar, G. L. (NIH, Bethesda, MD 20014) McIntire, K. R. *Fed Proc* 36(3): 1255; 1977. (no refs.)

77-1369 Stimulation of DNA Synthesis in the Lungs of Hamsters Exposed Intermittently to Nitrogen Dioxide. (Eng.) Creasia, D. A. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) Nettesheim, P.; Kim, J. C. *J Toxicol Environ Health* 2(5): 1173-1181; 1977.

Stimulation of [^3H]thymidine incorporation in the lungs of male Syrian golden hamsters exposed singly and repeatedly to 10 ppm nitrogen dioxide (NO_2) was studied. After 24 hr, a marked increase in [^3H]thymidine labeling took place in the bronchi, bronchioles, and alveolar ducts, but not in the trachea or the peripheral alveoli. Subsequent exposures to NO_2 repeated daily caused no further stimulation of [^3H]thymidine incorporation in any part of the respiratory tract unless an exposure-free interval between the first and subsequent exposures was allowed. After a 2-3-day interval, stimulation of [^3H]thymidine incorporation was observed in the bronchi, bronchioles, and alveolar ducts for up to 21 NO_2 exposures; when the interval between subsequent exposures was extended to 7 days, a significantly greater increase in [^3H]thymidine incorporation was observed. However, no repeated exposure was as effective as the first NO_2 exposure in stimulating incorporation of [^3H]thymidine. These data are noteworthy in light of the "tolerance phenomenon" documented in animals preexposed to an oxidant gas and subsequently protected from the lethal effects of later exposures. (13 refs.)

77-1370 Chromosome Tests with 134 Compounds on Chinese Hamster Cells in Vitro--A Screening for Chemical Carcinogens. (Eng.) Ishidate, M. (Dept. Chemical

Pathology, Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan) Odashima, S. *Mutat Res* 48(3/4): 337-353; 1977.

Chromosome aberrations were investigated in Chinese hamster cells cultured with carcinogenic N-nitroso compounds and their related derivatives, food additives, medical drugs, pesticides and other common industrial and laboratory chemicals. Growth inhibition tests were carried out preliminary to chromosome tests. Of the 134 chemicals, 63 gave negative results in the chromosome aberration test even at doses which markedly inhibited cell growth. Nearly all compounds known to be mutagenic in bacteria were also positive in the chromosome aberration tests. Urethane and diethylstilbestrol, known to be carcinogenic but not mutagenic in bacteria, were positive. Compounds such as N-alkyl-N-nitroguanidines, barbital, sodium benzoate, saccharin sodium, sodium nitrite, sodium nitrate and 4-aminoquinoline-1-oxide were positive but were not conclusively tested for carcinogenicity. (16 refs.)

77-1371 The Co-carcinogenic Activity of 4-Nitropyridine-1-oxide (4-NPO) and Prevention of Transformation by Type-specific Anti-viral Antibodies. (Eng.) Price, P. J. (Microbiological Associates-Torrey Pines Res. Center, 2945 Science Park Road, La Jolla, CA 92037) Auletta, A. E.; King, M. P.; Hugunin, P. M.; Huebner, R. J. *In Vitro* 12(8): 595-598; 1976.

Fischer rat embryo cells chronically infected with Rauscher murine leukemia virus (RLV) were transformed by the weak carcinogen 4-nitropyridine-1-oxide (4-NPO). Transformed cells grew in semisolid agar and produced tumors in newborn Fischer rats. Treatment of the cells with neutralizing antibody specific for the ecotropic RLV, prior to and during treatment with either 4-nitroquinoline-1-oxide or 4-NPO, prevented both transformation and the production of supernatant virus. Cells so treated were also nontumorigenic in the isologous host. Sister cultures were not protected by neutralizing antibody of equivalent low toxicity (produced against the AT-124 virus), which is specific for xenotropic murine viruses but does not neutralize RLV. These results demonstrate the critical role of the replicating C-type virus in cell transformation and indicate that this system (Fischer rat embryo cells chronically infected with RLV) is sensitive enough to show the transforming potential of a weak carcinogen. (13 refs.)

77-1372 Hycanthone: An Alkylating Agent. (Eng.) Miller, J. L. (Dept. Pharmaceutical Chemistry, Univ. Bradford, Bradford, BD7 1DP, England) Hulbert, P. B. *J Pharm Pharmacol* 28 (Suppl.): 18p; 1976.

Hycanthone, an alkylating agent, reacted with 4-(4-nitrobenzyl)-pyridine (NBP). Analysis of the product of this

reaction showed that attack of NBP occurs at the hydroxymethyl group of hycanthone. This implicates this chemical grouping in the biochemical mechanism of toxicity. The results suggest that hycanthone is bioactivated to a potent alkylating agent such as a reactive ester. (7 refs.)

77-1373 Pancreatic Carcinoma Induced by 4-Hydroxyaminoquinoline 1-oxide after Partial Pancreatectomy and Splenectomy in Rats. (Eng.) Konishi, Y. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara 634, Japan) Denda, A.; Inui, S.; Takahashi, S.; Kondo, H. *Gann* 67(6): 919-920; 1976.

The effect of 4-hydroxyaminoquinoline-1-oxide (4-HAQO) on male Wistar rats following partial pancreatectomy was investigated. 4-HAQO was administered iv 3 days after partial pancreatectomy. The results indicated that the regeneration induced by partial pancreatectomy enhanced 4-HAQO carcinogenesis in all the animals. (4 refs.)

77-1374 Mutagenic Effect of Sodium Arsenite in Chinese Hamster Cell Line Dede (Meeting Abstract). (Eng.) Rossner, P. (Inst. Hygiene and Epidemiology, Prague 100 42, Czechoslovakia) *Mutat Res* 46(3): 234-235; 1977. (no refs.)

77-1375 Mutagenic Effect of Heavy Metal Salts on Salmonella in Activation Systems in Vivo and in Vitro (Meeting Abstract). (Eng.) Kalinina, L. M. (Inst. General Genetics, USSR Acad. Science, Moscow, USSR) Polukhina, G. H. *Mutat Res* 46(3): 223-224; 1977. (no refs.)

77-1376 Further Considerations of Metal Carbonyls in Tobacco Smoke. (Eng.) Stahly, E. E. (Flammability News Bulletin, Inc., P. O. Box 13085, Washington, DC 20009) Lard, E. W. *Chem Ind* (2): 85-86; 1977.

The products of mechanically smoked cigars were analyzed for iron, nickel and cobalt. It was assumed that metals are carried into smoke as metal carbonyls formed in the cooler zones of the cigar behind the combustion. Metal carbonyls could not be isolated or identified in unsmoked cigars, ashes, butts or smoke. The metal content of these smoke products was determined and the metal carbonyl content of cigar smoke was calculated from these figures. It was concluded that the explanation of the volatilization of the transition metals in tobacco smoke is applicable to cigar tobacco. (8 refs.)

77-1377 **Relation Between Chemical Constituents of Tobacco and Mutagenic Activity of Cigarette Smoke Condensate.** (Eng.) Mizusaki, S. (Central Res. Inst., Japan Tobacco and Salt Corporation 6-2, Umeoka, Midori-ku, Yokohama, Kanagawa 227, Japan) Okamoto, H.; Akiyama, A.; Fukuhara, Y. *Mutat Res* 48(3-4): 319-325; 1977.

Mutagenic potency of cigarette smoke condensate was related to the content of nitrogenous substances in the tobacco. Smoke condensates obtained from 18 varieties of tobacco were assayed for mutagenesis in the presence of S-9 Mix (liver microsomal fraction prepared from polychlorinated biphenyl-injected rats) using *Salmonella typhimurium* TA 98. Of the nitrogenous constituents examined, total nitrogen and protein nitrogen and the soluble nitrogenous fraction were positively and significantly related to an increase in mutagenic activity of the smoke condensate, whereas nicotine and tartrate were not. Mutagenic potency of the condensate was lowest in leaves from the lower stalk position and increased with ascending leaf position on the stalk; this increase corresponded to the increase in nitrogenous constituents with the exception of nitrate. Smoke condensate from tobacco with higher sugar content had lower mutagenic activity. It is suggested that potent mutagenic nitrogen-containing compounds may be formed from proteins and amino acids during the burning of a cigarette. (21 refs.)

77-1378 **Correlated Effects of Cigarette Smoke Components on Alveolar Macrophage Adenosine Triphosphatase Activity and Phagocytosis.** (Eng.) Low, E. S. (Dept. Physiology and Biophysics, Univ. Vermont, Burlington, VT 05401) Low, R. B.; Green, G. M. *Am Rev Respir Dis* 115(6): 963-970; 1977.

Data are presented to support the hypothesis that cigarette smoke components affect pulmonary alveolar macrophage activities (such as adhesion and phagocytosis) by interfering with contractile protein function. A correlation was found between the effects of smoke components on phagocytosis and adenosine triphosphatase (ATPase) activities ascribed to contractile proteins. Acrolein inhibited phagocytosis, adhesion, and calcium-dependent ATPase activity, while ouabain and ethacrynic acid inhibited sodium-potassium-dependent ATPase activity. (42 refs.)

77-1379 **An Animal Model of Cigarette Smoking in Beagle Dogs. Correlative Evaluation of Effects on Pulmonary Function, Defense, and Morphology.** (Eng.) Berk, S. S. (Albert Einstein Coll. Medicine, Bronx Municipal Hospital Center, 1300 Morris Park Ave., Bronx, NY 10461) Nakagawa, Y.; Goldring, I. P.; Daly, M. M.; Zelefsky, M.; Spierer, M.; Morita, T. *Am Rev Respir Dis* 115(6): 971-979; 1977.

An animal model using beagle dogs was developed for evaluating the effect of chronic cigarette smoking on pulmonary defense and function and on lung structure. Moderate smoking impaired tracheal mucociliary transport and the bacteriosuppressive activity of alveolar macrophages. There was little change in pulmonary function. Dogs exposed to smoke showed subtle morphologic changes which consisted of areas of tracheal epithelial basal cell hyperplasia, an increase in the number of goblet cells in the large airways, and areas of peribronchiolar hypercellularity. (24 refs.)

77-1380 **Induction by Cigarette Smoke of Aryl Hydrocarbon Hydroxylase Activity in the Rat Kidney and Lung.** (Eng.) Van Cantfort, J. (Laboratoire de Chimie Medicale, Institut de Pathologie, Unite de Biochimie, B-4000 SART TILMAN par Liege 1, Belgium) Gielen, J. *Int J Cancer* 19(4): 538-545; 1977.

Characteristics of the induction of aryl hydrocarbon hydroxylase (AHH) activity in the rat kidney and lung by cigarette smoke are described. Rats exposed to a 1/15 dilution of cigarette smoke for 15 min showed increased AHH activity in the lung and kidneys. Enzymatic activity in the liver, bowel, testes, adrenal glands, brain, and skin were not affected. In the lung and kidney, AHH activity reached a peak approx 4 hr after smoke inhalation. The activity was three to four times that observed in unexposed rats. The hydroxylase activity decreased more rapidly in the kidney than in the lung. The lung enzyme was much more sensitive to cigarette smoke and reached max activity 4 hr after a 3-min exposure. Kidney enzyme was also induced, but to a much smaller extent. Successive inhalations, 2 hr apart, had an additive effect, and the max induced activity corresponded to an 8- to 12-fold induction. Experiments with cycloheximide and actinomycin D showed that protein synthesis is continuously required to induce AHH activity, but that RNA synthesis is only necessary in the initial period of induction. In vitro smoke induced AHH activities displayed sensitivity to the inhibitory action of α -naphthoflavone, metyraprone, SKF 525 A, and 2,5-diphenyloxazole. (44 refs.)

77-1381 **An Isolated Perfused Lung (IPL)-Smoke System for Studying the Inhibition of Benzo(a)pyrene (BAP) Metabolism by Smoke (Meeting Abstract).** (Eng.) Lubawy, W. C. (Coll. Pharmacy, Univ. Kentucky Medical Center, Lexington, KY 40506) Griffith, R. B.; Kostenbauder, H. B.; Perrier, D. *Fed Proc* 36(3): 970; 1977. (no refs.)

77-1382 **Organ Culture--A System for Rapid Carcinogenicity Screening of Tobacco Extracts on Oral Mucosa.** (Eng.) Gothoskar, S. V. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012,

India) Arjungi, K. N.; Tezabwala, B. U.; Taskar, S. P.; Ranadive, K. J. *Indian J Cancer* 13(3): 243-251; 1977.

Organ culture methods were devised for both human fetal buccal mucosa and rat oral mucosa, and the rat mucosa cultures were used for the in vitro carcinogenicity screening of tobacco extracts. The rat oral mucosa cultures were exposed for 7-18 days to extracts from three types of tobacco used in India: Mainpuri, Pattiwala, and Vadakkan tobaccos. Comparison cultures were exposed to 5 and 10 $\mu\text{g/ml}$ 9,10-dimethyl-1,2-benzanthracene (DMBA). Most of the cultures treated with Mainpuri and Vadakkan tobacco extracts showed loss of intercellular adhesion, irregular stratification, and basal cell hyperplasia. The hyperplasia was apparent as early as 7 days with the Mainpuri and 10 days with the Vadakkan tobacco extracts. Cultures treated with the Pattiwala tobacco extracts showed hyperplasia of the mucosal epithelium, with the formation of islands lined by a basal cell layer. These changes were not seen in 80%-90% of the untreated control cultures. The majority of the DMBA-treated cultures (12/18) showed irregular stratification and anisocytosis. Hyperplastic changes in the basal cell layer and loss of intercellular adherence were observed in 6/18 cultures. These studies indicate that oral mucosa organ cultures may be used successfully as a rapid in vitro screening method for carcinogenic effects. (29 refs.)

77-1383 Rat Mammary Tumor Growth, Cell Proliferation, and Differentiation Following Dibutyryl Cyclic AMP, Prostaglandins, and Estrogen Administration (Meeting Abstract). (Eng.) Klein, D. M. (Dept. Physiology, Univ. Illinois Coll. Medicine, Chicago, IL 60680) Loizzi, R. F. *Fed Proc* 36(3): 398; 1977. (no refs.)

77-1384 Absorption and Glucuronidation of Diethylstilbestrol by the Rat Small Intestine (Meeting Abstract). (Eng.) Lasker, J. (Dept. Pharmacology, Michigan State Univ., East Lansing, MI 48824) Rickert, D. E. *Fed Proc* 36(3): 1031; 1977. (no refs.)

77-1385 Elevated Serum Cathepsin B1 Activity with Vaginal Adenosis and Adenocarcinoma in Young Women Exposed in Utero to Diethylstilbestrol (Meeting Abstract). (Eng.) Pietras, R. J. (Dept. Biology, UCLA, Los Angeles, CA 90024) Szego, C. M.; Mangan, C. E.; Seeler, B. J.; Burtnett, M. M.; Orevi, M. *Fed Proc* 36(3): 387; 1977. (no refs.)

77-1386 Cytogenetic Studies and Diethyl Stilboestrol (Meeting Abstract). (Eng.) Bishun, N. P. (Tissue Culture and Cytogenetics Unit, Marie Curie Memorial

Foundation, The Chart, Oxted, Surrey, England) Smith, N. Eddie, H.; Williams, D. C. *Mutat Res* 46(3): 211-212; 1977. (no refs.)

77-1387 Significance of the Progesterone Receptor in the Estrogen-induced and -dependent Renal Tumor of the Syrian Golden Hamster. (Eng.) Li, S. A. (Dept. Medicine and Res. Service, Veterans Admin. Hosp., Minneapolis, MN 55417) Li, J. J.; Vilee, C. A. *Ann NY Acad Sci* 286: 369-383; 1977.

The progesterone receptor in the renal tumor cytoplasm was characterized and compared to its counterpart in the Syrian golden hamster uterus, and the role of progesterone in tumor induction and regression in the hamster kidney was investigated. Estrogen enhanced the progesterone-binding capacity of renal cytoplasmic fractions; after 2.5 mo of diethylstilbestrol (DES) treatment, the amount of specific 4S progesterone-binding component reached a plateau and remained a 17-fold higher level than that of untreated controls. This represents the earliest change reported thus far that occurs during the induction period of Syrian hamster renal tumor. With the appearance of renal tumor nodules, the amount of specific progesterone-binding activity increased dramatically in the kidney tumor, and it sedimented as a 7S to 8S receptor after sucrose gradient centrifugation. The sedimentation properties, binding affinity, and hormonal specificity of the progesterone receptor in the hamster renal tumor and in uterine cytosols were similar. Kidney tumor cytoplasm from animals treated with both progesterone and estradiol had slightly less available 8S estradiol receptor than did the cytoplasm of the renal tumor treated with estradiol alone. This suppression may be important in contributing to progesterone-induced renal tumor regression in the hamster. (32 refs.)

77-1388 Interaction of Estrogen-Receptor Complex (ER) with Uterine Nuclei (Meeting Abstract) (Eng.) Muller, R. E. (Boston Univ. Sch. Medicine, Boston, MA 02118) Traish, A.; Wotiz, H. H. *Fed Proc* 36(3): 911; 1977. (no refs.)

77-1389 Estrogen Receptors in Hamster Melanoma HM Mel 1 (Meeting Abstract). (Eng.) Snyder, J. (Div. Surgical Oncology, Univ. Illinois Medical Sch., Chicago, IL 60612) Das Gupta, T. K. *Fed Proc* 36(3): 349; 1977. (no refs.)

77-1390 Estrogen-Induced Changes in Stearyl-CoA Desaturase Activity in Chick Liver (Meeting Abstract). (Eng.) Lippiello, P. M. (Dept. Biochemistry, Univ. Virginia, Charlottesville, VA 22901) Holloway, C. T.; Garfield, S.; Holloway, P. W. *Fed Proc* 36(3): 789; 1977. (no refs.)

7-1391 **Hormone-Replacement Therapy and Endometrial Carcinoma (Letter to Editor).** (Eng.) Muirhead, W. (Hamilton Clinic, Ontario Cancer Foundation, Hamilton, Ontario L8V 1C3, Canada) *Lancet* 1(8025): 1309; 1977.

A review was conducted to examine the correlation between estrogen administration and endometrial carcinoma. The study indicated that exogenous estrogen causes hyperplasia that can be confused with grade I cancer invasion. It is suggested that review of material regarded as invasive disease should include the proportion of grade I to grades II and III cancers. (5 refs.)

7-1392 **Hepatic Adenomas and Focal Nodular Hyperplasia of the Liver in Young Women on Oral Contraceptives: Case Reports.** (Eng.) Jhingran, S. G. (Dept. Medicine, Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX 77030) Mukhopadhyay, A. K.; Ajmani, S. K.; Johnson, P. C. *J Nucl Med* 18(3): 263-266; 1977.

Two cases of hepatic adenoma and one of focal nodular hyperplasia occurred in three women (29, 32, and 35 yr old) who had been taking oral contraceptives for 3-4 yr. One of the hepatic adenoma patients and the nodular hyperplasia patient had a total asymptomatic presentation. The other patient presented with abdominal pain, diarrhea, chills, and fever. The two adenoma patients had significant bleeding in and around the tumor, but there was no change in SGOT, GPT, or bilirubin. Two of the three women had angiographic examinations that indicated the position and size of the tumors clearly, and they correlated well with the scintigraphic localization. For max diagnostic accuracy, hepatic scanning should be correlated with the clinical, angiographic, and histologic data. The possibility of hepatic adenoma and focal nodular hyperplasia should be considered in any young woman taking oral contraceptives who has clinical manifestations such as acute or chronic right upper quadrant pain, unexplained blood loss, and anemia. (21 refs.)

7-1393 **Oral Contraceptives and Breast Lesions (Letter to Editor).** (Eng.) Fasal, E. (Cancer Control, Dept. Health, State of California--Health and Welfare Agency, 1252 Berkeley Way, Berkeley, CA 94704) Paffenbarger, S. *J Natl Cancer Inst* 58(1): 12; 1977.

The use of oral contraceptives by women with a history of benign breast disease is discouraged. The data show that women with a history of prior biopsy for benign breast disease who had taken oral contraceptives for > 6 yr had an eightfold increase in the risk of developing breast cancer compared to similar women who had never used oral contraceptives. Continued study is warranted, but oral contraceptives should not be prescribed for patients with prior or present benign breast disease. (no refs.)

77-1394 **Oral Contraceptives and Breast Lesions (Letter to Editor).** (Eng.) Hatcher, R. A. (Family Planning Program, Dept. Gynecology and Obstetrics, Emory Univ. Sch. Medicine, 69 Butler St., S.E., Atlanta, GA 30303) *J Natl Cancer Inst* 58(1): 12; 1977.

The use of oral contraceptives for the treatment of benign breast disease is discussed. Women with prior biopsy for benign breast disease were more likely to develop breast cancer if they used oral contraceptives, for long periods of time. Clinically, benign diseases are now being treated with oral contraceptives. The predilection of physicians to treat severe fibrocystic disease with oral contraceptives rather than just using the pills as contraceptive agents themselves may have caused the increased risk of developing breast cancer in women with benign breast disease. Until this point is clarified, the treatment of fibrocystic disease with oral contraceptives should be discontinued. (1 ref.)

77-1395 **Effect of Prednisone on Acetaminophen Metabolism in Tumor Bearing Rats (Meeting Abstract).** (Eng.) Bolanowska, W. (Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY 14263) Gessner, T. *Pharmacologist* 18(2): 160; 1977. (no refs.)

77-1396 **Reduction by Pituitary Grafts of Mammary Tumor Age. Its Variability in a High Mammary Tumor Strain of Mice: Effects on Mammary DNA Synthesis (Letter to Editor).** (Eng.) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan) Yanai, R.; Taniguchi, H. *Eur J Cancer* 12(12): 1017-1019; 1976.

The effect of pituitary grafts on DNA synthesis and tumor development in the mammary glands was studied in mammary-tumor-susceptible SHN virgin mice. At 20-23 days of age, half of the females in each litter received two isologous pituitary grafts under the right kidney capsule. The other half received no treatment and served as controls. The mice were checked every 7 days for palpable mammary tumors. At 70 days of age, mice from both groups were given ip injections of ³H-thymidine, and 2 hr later the amount incorporated into mammary DNA was assayed as an index of mammary DNA synthesis. Tumor incidences were 95.9% in the experimental group and 88.5% in the control group. In the graft mice, tumors developed at an average of 5.9 mo in 36% and within 1 mo before and after the average in 70%. In the controls the peak age for tumor development was 8.9 mo, at which time 20% had developed tumors. The rate of mammary DNA synthesis at 70 days of age varied between 120 and 400 disintegrations per minute (dpm)/μg DNA and between 13 and 710 dpm/μg DNA in the experimental and control groups, respectively. The longer the period of high mammary DNA synthesis, the higher the probability of malignant transformation of the mammary cells. The data support the hypothesis that hor-

mone stimulation of the mammary gland can create conditions favorable for the action of carcinogens. (12 refs.)

77-1397 Estrogenically-Active Forms of o,p'-DDT and Methoxychlor (Meeting Abstract). (Eng.) Nelson, J. A. (Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL 35205) Struck, R. F.; James, R. *Pharmacologist* 18(2): 247; 1977. (3 refs.)

77-1398 Effects of Saccharin on Renal Tubular Transport of Organic Ions in Adult Female Rats (Meeting Abstract). (Eng.) Goldstein, R. (Michigan State Univ., East Lansing, MI 48824) Hook, J. B.; Bond, J. T. *Fed Proc* 36(3): 1116; 1977. (no refs.)

77-1399 Cyclophosphamide and Malignancy (Letter to Editor). (Eng.) Puri, H. C. (Dept. Pediatrics, Health Sciences Center, Univ. Oregon, Portland, OR 97201) Campbell, R. A. *Lancet* 1(8025): 1306; 1977.

A 13-yr-old girl with glomerulonephritis was treated with 12 g of cyclophosphamide over 3 mo. She developed cystosarcoma phylloides of the breast and carcinoma in situ of the uterine cervix, simultaneously, 9 yr later. A literature search coupled with findings indicated that the risk/benefit ratio for cyclophosphamide needs revision. (3 refs.)

77-1400 Chromosome Aberrations Produced in Vivo by Chemicals (Meeting Abstract). (Eng.) Dobos, M. (2nd Dept. Pediatrics, Semmelweis Univ. Medical Sch., Budapest, Hungary) Fekete, G.; Schuler, D.; Szakmary, E. *Mutat Res* 46(3): 216; 1977. (no refs.)

77-1401 The Cytogenetic Basis of Dominant-Lethal Mutations in Mice: Studies with TEM, EMS, and 6-Mercaptopurine (Meeting Abstract). (Eng.) Matter, B. E. (Biological and Medical Res. Div., Sandoz Ltd., Basel, Switzerland) Jaeger, I. *Mutat Res* 46(3): 230; 1977. (2 refs.)

77-1402 Attempt to Develop an In Vitro DNA Repair System with Human Enzymes: Demonstration of Nick Translation (Meeting Abstract). (Eng.) Bose, K. (Univ. Chicago, Chicago, IL 60637) Karran, P.; Strauss, B. *Fed Proc* 36(3): 885; 1977. (no refs.)

77-1403 Regulation of DL-Ethionine Metabolism in Rats In Vivo (Meeting Abstract). (Eng.) Brada, Z. (Papanicolaou Cancer Res. Inst., Miami, FL 33123) Bulba, S. *Fed Proc* 36(3): 1074; 1977. (no refs.)

77-1404 In Vitro Transformation of Human Cells by N-Hydroxyurethan & Urethan-DNA Complex (Meeting Abstract). (Eng.) Ranadive, K. J. (Div. Biology Cancer Res. Inst., Bombay, India) Talageri, V. R.; Bhide, S. V. *Ind J Biochem Biophys* 14(1/Suppl): 27; 1977. (no refs.)

77-1405 Toxicity of Anti-Carcinogenic Retinoids in Organ Culture. (Eng.) Bard, D. R. (Strangeway Res. Lab., Wort's Causeway, Cambridge CB1 4RN, England) Lasnitzki, I. *Br J Cancer* 35(1): 115-119; 1977.

Studies to determine the effect of synthetic vitamin A analogues on sulfate-labeled protein polysaccharides and on metaphase chromasia in rabbit ear cartilage in organ culture are reported. All compounds with carboxylic acid groups were active in inducing release of sulfate and loss of metaphase chromasia; compounds in which the acid moiety was replaced by less hydrophilic groups had diminished activity. The results support the hypothesis that retinoic acid may act as a detergent by destabilizing lysosomal membranes. (13 refs.)

77-1406 Occurrence of Isoenzymes of Arginase in Mouse Lung Tumour. (Eng.) Kesava Rao, K. V. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012, India) Talageri, V. R.; Bhide, S. V. *Indian J Biochem Biophys* 13(3): 239-241; 1976.

Lung tumors were induced in male Swiss mice by hydrazine sulfate. The arginase activity was increased about tenfold in lung tumors as compared to normal untreated lung tissue. When the arginase fraction was isolated from lung tumor and subjected to DEAE-cellulose chromatography and polyacrylamide gel electrophoresis, two peaks were obtained. These two fractions indicate the presence of two corresponding isoenzymes in lung tumors. (11 refs.)

77-1407 Nitrogen Intake and Tumorigenesis in Rats Injected with 1,2-Dimethylhydrazine. (Eng.) Topping, D. C. (Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN 37830) Visek, W. J. *J Nutr* 106(11): 1583-1590; 1976.

Cancer incidence was evaluated in 1,2-dimethylhydrazine (DMH)-injected rats fed graded concentrations of dietary protein with and without supplemental urea. Weanling male Sprague-Dawley rats were inoculated with 15 mg/kg/w

DMH for 24 wk and fed isoenergetic casein-sucrose diets containing 7.5%, 15%, or 22.5% protein with or without 2.5% urea. Rats fed 15% and 22.5% protein had a greater number of DMH-induced tumors in their intestines at 32 wk. Ear tumors were also greater in number and evident earlier (21 wk) in rats fed 22.5% protein compared to the other groups. Whether the reduced number of tumors in rats fed 7.5% protein was due to suboptimal protein intake during the period of rapid body growth could not be determined. Urea feeding did not increase the number of tumors in the colon or rectum, and it did not cause changes in pH, urease activity, or ammonia concentration of the contents or changes in blood cholesterol. As dietary protein increased, cecal ammonia concentrations, portal blood urea, and cholesterol rose and both colon and cecal pH dropped. DMH-treated rats had significantly higher concentrations of colon and cecal ammonia and lower blood cholesterol. The lack of enhanced carcinogenesis with urea in the diet at each protein level argues against ammonia playing a significant role in the process. (41 refs.)

77-1408 **Procarbazine-Induced Specific Locus Mutations in Male Mice (Meeting Abstract).** (Eng.) Helling, U. H. (Gesellschaft für Strahlen- und Umweltforschung, Abteilung für Genetik, D-8042 Neuherberg, W. Germany) Neuhauser, A. *Mutat Res* 46(3): 218; 1977. (1 ref.)

77-1409 **Mutagenic Studies with Acrylonitrile.** (Eng.) Milvy, P. (Mount Sinai Sch. Medicine, City Univ. New York, NY 10029) Wolff, M. *Mutat Res* 48(3-4): 21-278; 1977.

The Ames *Salmonella typhimurium*/liver microsome assay system was used to demonstrate the mutagenicity of acrylonitrile (AN, vinyl cyanide, propenenitrile) in the TA 1535, TA 98 and TA 978 strains. Three procedures were used: spotting the AN on a "lawn" of *Salmonella*, shaking a reaction mixture consisting of bacteria, liver homogenate and AN, and exposing the homogenate and bacteria to an atmosphere containing AN. Mutagenesis by this latter method was observed at exposures as low as 57 ppm; 20 ppm is the current threshold limit value for AN in the U.S. It is suggested that more extensive animal studies be implemented to determine the carcinogenic potential of AN. (29 refs.)

77-1410 **Mutagenicity of Acrylonitrile in Bacteria (Meeting Abstract).** (Eng.) Venitt, S. (Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Chertingales Lane, Chalfont St. Giles, Bucks, HP 8 4SP, England) Bushell, C. T. *Mutat Res* 46(3): 241; 1977. (no refs.)

77-1411 **Vinyl Chloride (VCM): An Example for Evaluating Adverse Biological Effects in Short-Term Tests (Meeting Abstract).** (Eng.) Bartsch, H. (International Agency for Res. on Cancer, Lyon, France) Loprieno, N. *Mutat Res* 46(3): 200-201; 1977. (no refs.)

77-1412 **Inhalation Toxicity of Vinyl Chloride (VC) or Vinylidene Chloride (VDC) in Rats and Mice (Meeting Abstract).** (Eng.) Lee, C. C. (Midwest Res. Inst., Kansas City, MO 64110) Bhandari, J. C.; House, W. B.; Peters, P. J.; Woods, J. S.; Dixon, R. L. *Pharmacologist* 18(2): 245; 1977. (2 refs.)

77-1413 **Mutagenicity Testing of Urine from Vinylchloride (VCM) Treated Rats Using the *Salmonella* Test System (Meeting Abstract).** (Eng.) Mattern, I. E. (Medical Biological Lab. TNO, Rijswijk, The Netherlands) van der Zwaan, W. B.; Willems, M. J. *Mutat Res* 46(3): 230-231; 1977. (no refs.)

77-1414 **A Teratologic Evaluation of Plasma-Soluble Extracts of Polyvinyl Chloride Plastics (Meeting Abstract).** (Eng.) Garvin, P. J. (Baxter Travenol Lab., Morton Grove, IL 60063) Lewandowski, M. E.; Wallin, R. F. *Pharmacologist* 18(2): 231; 1976. (no refs.)

77-1415 **Plasticizer Disposition in a Conscious Patient (Meeting Abstract).** (Eng.) Peck, C. C. (Letterman Army Inst. Res., San Francisco, CA 94129) Bailey, F. J.; Odom, D. G.; Blatt, H. D.; Barrett, B. B. *Pharmacologist* 18(2): 195; 1976. (no refs.)

77-1416 **Population Cytogenetic Study of Mutagenic Effect of Epichlorohydrin (Meeting Abstract).** (Eng.) Kucerovala, M. (Genetic Lab., Inst. Hygiene and Epidemiology, Prague Pediatric Dept., Postgraduate Medical Inst., Prague, Czechoslovakia) Zhurkov, V. S. *Mutat Res* 46(3): 227-228; 1977. (no refs.)

77-1417 **Continuous Inhalation of 1,1-Dichloroethylene (DCE) by Rats and Mice During Gestation (Meeting Abstract).** (Eng.) Short, R. D. (Midwest Res. Inst., Kansas City, MO 64110) Minor, J. L.; House, W. B.; Marcus, W.; Lee, C. C. *Pharmacologist* 18(2): 245; 1977. (no refs.)

77-1418 Comparative Enzyme Induction and Lindane Metabolism in Rats Pre-treated with Various Organochlorine Pesticides. (Eng.) Chadwick, R. W. (Biochemistry Branch, Environmental Toxicology Div., Health Effects Res. Lab., Environmental Res. Center, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711) Chadwick, C. J.; Freal, J. J.; Bryden, C. C. *Xenobiotica* 7(4): 235-246; 1977.

The comparative effect of pretreatment for 7 days with pesticides on the metabolism of lindane in vivo and on the activity of various rat liver microsomal enzymes in vitro was investigated in weanling female Holtzman rats. The animals received daily po injections of arachis oil containing 1 mg of either chlordane, DDT, hexachlorobenzene (HCB), mirex, penphene, pentac, toxaphene, or arachis oil alone. All animals received 1.7 mg lindane on the eighth day, and they were sacrificed 24 hr later. Mirex was the most potent inducer of the oxidative hydrolysis of O-ethyl-O-p-nitrophenylphenylphosphonothioic acid, the O-demethylation of p-nitroanisole, and the azo reduction of methyl orange. Chlordane and DDT were equipotent, followed by HCB, toxaphene, pentac, and penphene. The enzyme activity of rats pretreated with the latter three pesticides was not significantly higher than that of controls. DDT pretreatment stimulated a greater metabolism of lindane than did any of the other six pesticides. The most effective activators of lindane were DDT, mirex, chlordane, and HCB. It is concluded that comparative differences in lindane metabolism in vivo are not adequately reflected by determination of enzyme activities in vitro and that pretreatment with organochlorine pesticides alters lindane metabolism by selective effects on specific metabolic pathways. (20 refs.)

77-1419 Pilot Study of the Mutagenicity of DDT in Mice. (Eng.) Wallace, M. E. (Dept. Genetics, Milton Road, Cambridge CB4 1XH, England) Knights, P.; Dye, A. O. *Environ Pollut* 11(3): 217-222; 1976.

An inbred strain of CF/1 mice, half of which had been given a diet containing 250 ppm of DDT over five generations and half of which were untreated, was investigated to find whether there was a greater incidence of mutants in the treated than in the control mice. There were 30 individuals, occurring at random between the sexes and over the four main groups of matings, that demonstrated physical abnormalities. Two

mice, one with a gross limb malformation and one with a hind legs, occurred in the treated stocks. The rest all had small defects, such as a bifurcated left or right ear, tail kink, or unusually small body size. Of the 42 females of each stock outcrossed to test for color and other mutants, 3 proved to be black-and-tan rather than nonagouti. All three occurred in the treated stock. From the 170 females in each stock autopsied at 16 days' gestation, several exencephalic young were seen. These also occurred only in the treated stock, there being 12 matings segregating in this anomaly. Although there were two recessive visibles in the treated and none in the control mice, there is no evidence for a greater incidence of recessive invisibles in the treated half. There is concluded to be no case for a grossly mutagenic effect of DDT. (11 refs.)

77-1420 Uptake and Metabolism of Pesticides by the Isolated Perfused Rat Lung (Meeting Abstract). (Eng.) Abou-Donia, M. B. (Dept. Physiology, Duke University Medical Center, Durham, NC 27710) Charles, J. M.; Menze, D. B. *Pharmacologist* 18(2): 247; 1977. (no refs.)

77-1421 Aldrin Toxicity in Mammalian Cells (Meeting Abstract). (Eng.) DeVore, D. P. (Battelle Columbus Lab., Columbus, OH 43201) Sheridan, M. A.; Prideman, J. S.; Hutson, T. B. *Pharmacologist* 18(2): 245; 1977. (1 ref.)

See also:

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PHYSICAL CARCINOGENESIS

77-1422 Radiation Effects on Cancer Mortality Among A-Bomb Survivors, 1950-1972: Comparison of Some Statistical Models and Analysis Based on the Additive Logit Model. (Eng.) Otake, M. (Dept. Zoology, Faculty Science, Hiroshima Univ., Hiroshima 730, Japan) *J Radiat Res (Tokyo)* 17(4): 262-321; 1976.

Various statistical models designed to determine the effects of radiation dose on the mortality of atomic bomb survivors in Hiroshima and Nagasaki from specific cancers were evaluated to determine which is most appropriate for analysis of the radiation carcinogenesis data in a basic contingency table. On the basis of this evaluation, the additive logit model was selected to analyze the mortality of this population from October 1950 through December 1972. Leukemia mortality showed a sharp rise with increase in dose. A high mortality risk due to radiation was observed in survivors with doses of ≥ 200 rads for all cancers except leukemia, gastrointestinal tract cancer, lung cancer, and respiratory system cancer. During the period 1965-1972, a significant risk was also noted for stomach and breast cancers. Survivors who were ≤ 9 yr at the time of exposure and were exposed to doses of > 200 rads showed a high mortality risk due to all cancers except leukemia. There was a difference in dose response of leukemia between the two cities, which was due to the difference in neutron component between the two bombs. This suggests the possibility of estimating the relative biological effectiveness (RBE) of neutrons, and it indicates that the RBE is higher for survivors who were exposed at a low dose. (55 refs.)

77-1423 A Survey of Radiation Doses Received by Atomic-Bomb Survivors Residing in the U.S. (Eng.) Kerr, G. D. (Health Physics Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) Yamada, H.; Marks, S. *Health Phys* 305-313; 1976.

A survey was conducted of 300 of the estimated 500-750 survivors of the atomic bombings in Hiroshima and Nagasaki who now reside in the US. The ratio of women to men in this group was about 4:1. Almost 2/3 survivors were 10-25 yr old at the time of exposure. In Hiroshima, both neutrons and gamma rays contributed significantly to radiation exposure, but in Nagasaki, exposure was almost exclusively from gamma rays. Dose estimates for survivors in the proximal group (within 2,500 meters of the hypocenter) ranged from < 1 to 190 rads in Nagasaki and 510 rads in Hiroshima. Dose estimates from both local fallout of fission products and early entry into areas adjacent to the hypocenters could be made only in terms of ranges below upper limits (up to 10 rad in Hiroshima and 50 rad in Nagasaki), due to uncertainties in the available data. Health risks associated with radiation exposure were not discussed. (40 refs.)

77-1424 Cytogenetic Investigation of Persons Exposed Chronically to Ionizing Radiations (Meeting Abstract). (Eng.) Anger, H. (Staatliches Amt für Atomicherheit und Strahlenschutz der DDR, Berlin, E. Germany) Witkowski, R. *Mutat Res* 46(3): 27-28; 1977. (no refs.)

77-1425 Dermatologic Radiotherapy and Thyroid Cancer. (Eng.) Goldschmidt, H. (Suite 620, One Bala-Cynwyd Plaza, Bala-Cynwyd, PA 19004) *Arch Dermatol* 113(3): 362-364; 1977.

Procedures are outlined for the follow-up of patients with a history of neck or head irradiation for benign skin diseases. Palpation of the thyroid gland and surgical removal of discrete nodules are emphasized. Thyroid scans, which are not mandatory, should be performed with the technetium-99 scintigram, which delivers a lower radiation dose than the radioactive imaging procedure with ^{131}I . (14 refs.)

77-1426 Radiation-induced Peritoneal Mesothelioma. (Eng.) Babcock, T. L. (General Surgery Service, Letterman Army Medical Center, Presidio San Francisco, San Francisco, CA 94129) Powell, D. H.; Bothwell, R. S. *J Surg Oncol* 8(5): 369-372; 1976.

The case of a 55-yr-old woman who developed peritoneal mesothelioma 7 yr after internal and external irradiation in 1967 for Stage 1 carcinoma of the cervix is presented. In June 1974, the patient presented with symptoms of a partial bowel obstruction. She stated that she had intermittently had abdominal pain, nausea, and vomiting for 6 mo. At exploratory laparotomy, the patient was found to have a matted, almost completely obstructed, terminal ileum with dense adhesions to the right fallopian tube and ovary. She underwent resection of the terminal ileum, right colon, right fallopian tube, and ovary en bloc, with reestablishment of intestinal continuity by ileotransverse colostomy. Pathologic examination of the specimen demonstrated a mesothelioma. Four months later, the patient complained of increasing constipation and abdominal bloating. At reexploration, she was found to have a diffuse ip mesothelioma with distal colonic obstruction. The patient underwent palliative transverse colostomy. Postoperatively, she continued on a downhill course and died 3 mo later despite chemotherapy with procarbazine. No previous reports of tumor induction by irradiation have been found. (7 refs.)

77-1427 Effect of Wide Field Irradiation on Unirradiated Tumors in the Same Host (Meeting Abstract). (Eng.) Cooper, J. S. (New York Univ. Medical Cen-

ter, Div. Radiation Oncology, New York, NY) Bart, R. S.; Kopf, A. W.; Newall, J. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 107; 1976. (no refs.)

- 77-1428 **Chronic Myelogenous Leukemia Linked to Radiation Exposure.** (Eng.) Anonymous *NY State J Med* 77(2): 169-170; 1977.

A survey of 327 patients treated for chronic myelogenous leukemia (CML) between 1914-1975 revealed 29 patients with a history of radiation treatment (6 for malignant disease and 13 for nonmalignant conditions). The mean interval between radiation exposure and diagnosis of CML in the 29 patients was 14.6 yr. (no refs.)

- 77-1429 **Pancreatic Carcinoma as a Sequel to Therapy of Lymphoma.** (Eng.) Jochimsen, P. R. (Dept. Surgery, Univ. Iowa Hosps. and Clinics, Iowa City, IA 52242) Pearlman, N. W.; Lawton, R. L. *J Surg Oncol* 8(6): 461-464; 1976.

A pancreatic carcinoma occurred in a 31-yr-old man who, 5 yr previously, had undergone intensive radiotherapy and subsequent chemotherapy for treatment of a lymphoma. In 1970, following metastatic evaluation and staging laparotomy, the patient was classified as having a poorly differentiated nodular lymphocytic lymphoma, Stage III, with involvement of the spleen and the periaortic and cervical nodes. A mantel encompassing the mediastinum, the neck, and Waldeyer ring was used to deliver 3,400 rads, and the abdominal involvement was treated with an inverted Y plus a splenic tag, which delivered 4,000 rads. Periodically thereafter, lymph node enlargement in various locations appeared, and chemotherapy was employed. In 1975, a rock-hard mass was found in the head of the pancreas, with no other lymphadenopathy in the abdomen. A choledochoduodenostomy and transduodenal needle biopsy of the mass were done. Post-operatively, permanent sections demonstrated poorly differentiated adenocarcinoma of the pancreas. Because of induration and apparent tumor invasion of the superior mesenteric vessels, resection was not possible. The increased use of high-dose radiotherapy, particularly in conjunction with chemotherapy, for a first tumor may be directly related to the development of a second, and it is imperative that such an association be kept in mind. (9 refs.)

- 77-1430 **Radiation-Induced Changes in the Movement of Immunoglobulin Complexes on the Surface of B Cells (Meeting Abstract).** (Eng.) Anderson, R. E. (Univ. New Mexico, Albuquerque, NM 87131) Pogue, L. E. *Fed Proc* 36(3): 1089; 1977. (no refs.)

- 77-1431 **T Cell Depletion and Tumor Metastasis (Meeting Abstract).** (Eng.) Peters, L. J. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030) McBride, W. H.; Mason, K. A. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 106; 1976. (no refs.)

- 77-1432 **Effect of Low Exposure-Rate Gamma Irradiation on T and B Lymphocyte Function in the Mouse (Meeting Abstract).** (Eng.) McDermott, C. E. (Oak Ridge Associated Univ., Oak Ridge, TN 37830) Gengozian, N. *Fed Proc* 36(3): 1231; 1977. (no refs.)

- 77-1433 **Chromosome Aberration Yields Induced in Human Lymphocytes by 15 MeV Electrons Given at a Conventional Dose-Rate and in Microsecond Pulses.** (Eng.) Purrott, R. J. (Natl. Radiological Protection Board, Harwell, Didcot, Oxon OX11 0RQ, England) Reeder, E. J.; Lovell, S. *Int J Radiat Biol* 31(3): 251-256; 1977.

Yields of unstable chromosome aberrations were analyzed in human venous blood lymphocytes exposed to seven doses (44-742 rads) of 15-million-electron-volt electrons at an average dose rate of 100 rads/min and to eight doses (53-764 rads) delivered in microsecond pulses. No significant difference could be found between the two sets of data when they were analyzed in terms of the quadratic model of aberration production. Good agreement was observed with previous dose response studies in the same laboratory, in which human lymphocytes were exposed to 250-kilovolt x-rays and ^{60}Co x-rays at conventional rates of 100 and 50 rads/min, respectively. When taken in conjunction with other low-LET (linear energy transfer) data, these findings indicate that aberration yield is independent of dose rate over the following wide ranges: 25 to 6×10^3 , 100 to 1.5×10^{10} , and 150 to 3×10^{10} rads/min, respectively, for doses of 100, 250, and 500 rads. (15 refs.)

- 77-1434 **Megavoltage Radiation Oncogenesis in a Pediatric Population (Meeting Abstract).** (Eng.) Haselow, R. W. (Dept. Therapeutic Radiology, Pathology and Pediatrics, Univ. Minnesota Hosp., Minneapolis, MN) Dehner, L.; Nesbit, M.; Levitt, S. H. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 48-49; 1976. (no refs.)

- 77-1435 **Upper Limits of α -Radioactivity Per Particle of Cigarette Smoke.** (Eng.) Mogro-Campero, A. (General Electric Res. and Development Center, P.O. Box 8, Schenectady, NY 12301) Fleischer, R. L. *Health Phys* 32(1): 39-40; 1977.

The upper limits of α -activity per particle of cigarette smoke were determined. The upper limits were calculated by assuming that immediately after the smoking process the only radioactive element leading to α -emission was either ^{210}Po or ^{210}Pb . It was concluded that none of the smoke particles could have had more than 3×10^{-5} pCi of ^{210}Po or 1×10^{-4} pCi of ^{210}Pb . The results imply that the ^{210}Pb content of a few tobacco trichomes can be incorporated into one radioactive smoke particle. (4 refs.)

77-1436 Radiation Influenced Osteogenic Sarcoma of C₃H Mouse: Natural History, TCD₅₀ Assay and Influences of WB1 and *Corynebacterium Parvum* on These Parameters (Meeting Abstract). (Eng.) Choi, C. H. (Edwin L. Steele Lab. Radiation Biology, Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA) Sedlacek, R.; Suit, H. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 45; 1976. (no refs.)

77-1437 Radiation Cancer, Safety Standards and Current Levels of Exposure. (Eng.) Mole, R. H. (MRC Radiobiology Unit, Harwell, Oxon OX11 ORD, England) *INSERM* 52: 191-204; 1976.

The adequacy of safety standards and current levels of exposure to radiation are discussed in terms of cancer induction. Radiation-induced cancer originates only in directly irradiated tissues and its frequency is dose-dependent. The working hypothesis underlying all current radiation safety standards is that cancer induction is proportional to radiation dose. However, the simplest kind of empirical data on cancer frequency, ie, those after single brief exposures, often do not fit an uncomplicated linear regression on dose. A defensible overall linear coefficient for risk estimation is suggested as 100 cases of cancer of all types per million persons for uniform exposure of all body tissues to one rate of low linear energy transfer radiation. Observations on cancer in humans seem to provide good evidence against the existence of a threshold dose for carcinogenesis. Based on current levels of exposure to radiation from various sources in the United Kingdom and according to the linear hypothesis, in terms of the number of cancer cases in the population, the natural background of the environment appears to be 5 times more dangerous as a carcinogen than the routine practice of medicine, and the latter is at least 25 times more dangerous than all kinds of occupational exposure taken together. (15 refs.)

77-1438 Levels of Cyclic AMP Phosphodiesterase in X-Irradiation Induced Small Bowel Adenocarcinoma (Meeting Abstract). (Eng.) Lawson, A. J. (Radiation Res. Lab., Univ. Iowa, Iowa City, IA 52242) Stevens, R. H.;

Osborne, J. W.; Smith, D. D.; Oberley, L. W. *Fed Proc* 36(3): 347; 1977. (no refs.)

77-1439 The Effect of Ultraviolet Irradiation on Cyclic Nucleotide Concentrations in Human Diploid Fibroblasts (Meeting Abstract). (Eng.) Tejwani, G. A. (Dept. Pharmacology, Ohio State Univ. Coll. Medicine, Columbus, OH 43210) Fertel, R.; Hart, R. W. *Fed Proc* 36(3): 688; 1977. (no refs.)

77-1440 Cellular Aspects of Phototoxic Reactions Induced by Kynurenic Acid. I. Establishment of an Experimental Model Utilizing In Vitro Cultivated Cells. (Eng.) Wennersten, G. (Dept. Dermatology, Karolinska sjukhuset, S-10401 Stockholm 60, Sweden) Brunk, U. *Acta Derm Venerol (Stockh)* 57(3): 201-209; 1977.

The photooxidative damage induced by kynurenic acid was investigated in normal diploid human glia cells cultivated in vitro. Kynurenic acid alone retarded cell growth at a concentration of 5.29×10^{-3} M, as did a long exposure (2.4×10^{-3} sec) to long-wave UV light. Irradiation (0.6×10^3 sec) performed immediately after the addition of 5.29×10^{-4} kynurenic acid resulted in only a slight inhibition of cell growth. However, increased growth inhibition was observed in cells exposed to the same concentration of acid for 24 hr before irradiation. Scanning electron microscopy revealed that cells were uniformly damaged following exposure to both kynurenic acid and longwave UV light. Typical changes consisted of shrinkage, rounding up of the cells, and the formation of cytoplasmic blebs on the cell surface; the blebs appeared to originate in the microvilli and ruffling membranes. Increases in the kynurenic acid concentration and/or light dose resulted in augmented cell damage. Further study is required to elucidate the cellular mechanisms of the observed alterations. (30 refs.)

77-1441 The Effect of Ultraviolet Light (UVL) on the Lysosomes of Hairless Mouse Epidermis. (Eng.) Grossie, V. B. (Dept. Dermatology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX 77211) Black, H. S. *Experientia* 33(4): 425-426; 1977.

The effect of both acute and chronic exposure to UV light on the lysosomal membrane of hairless mouse epidermis was studied. The acid phosphatase activity from the skin of hairless mice given 10 times the minimal erythema dose (MED) was considerably less than that observed in the controls. When 5 MED was given, an increase in the activity occurred. The results indicate that the stability of the lysosomal membrane is decreased when the hairless mouse is exposed to UV irradiation. (18 refs.)

77-1442 **Biological Effects of Repeated Inhalation Exposure of Syrian Hamsters to $^{144}\text{CeO}_2$** (Meeting Abstract). (Eng.) Lundgren, D. L. (Inhalation Toxicology Res. Inst., Lovelace Res. Inst., Albuquerque, NM 87115) Hahn, F. F.; McClellan, R. O. *Radiat Res* 70(3): 639-640; 1977. (no refs.)

77-1443 **The Disposition of Americium-241 Oxide Following Inhalation by Beagles** (Meeting Abstract). (Eng.) Craig, D. K. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA 99352) Park, J. F.; Powers, G. J.; Catt, D. L. *Radiat Res* 70(3): 639; 1977. (no refs.)

77-1444 **Measurement of Polonium Activity in Indian Tobacco.** (Eng.) Singh, D. R. (Div. Radiological Protection, Bhabha Atomic Res. Centre, Trombay, Bombay 400 085, India) Nilekani, S. R. *Health Phys* 31(4): 393-394; 1976.

Typical Indian tobacco products were analyzed for polonium-210 content. Indian cigarettes contained from 0.07 to 0.10 pCi/g of ^{210}Po , cheroots contained 0.065 pCi/g, small cigars contained 0.052 pCi/g, larger cigars 0.025 pCi/g, beedi filling 0.081 pCi/g, and soil contained 0.30 pCi/g ^{210}Po . From the above data it was estimated that the ^{210}Po lung burden of an Indian cigarette smoker was 23.6 millirads/day. This is 3-6 times higher than that due to natural background radiation in the atmosphere. (5 refs.)

77-1445 **High Absorption Efficiency for Ingested Plutonium in Crabs.** (Eng.) Fowler, S. W. (International Lab. Marine Radioactivity, Musee Oceanographique, Monaco) Guary, J. C. *Nature* 266(5605): 827-828; 1977.

The fate of plutonium in a single, worm-crab food chain after ingestion of the isotope which had been metabolically incorporated into the predator's food was studied. It was discovered that ^{237}Pu naturally incorporated into food can be assimilated into the predator's tissues with efficiencies several orders of magnitude higher than those characteristic of mammalian systems. In the crab, concentrations of residual ^{237}Pu were highest in the hepatopancreas, with less in the gills, stomach, shell, and muscle. Data indicating extremely low gastrointestinal absorption of plutonium by vertebrates are not applicable to species comprising the bulk of the marine biomass. (20 refs.)

77-1446 **The Uptake, Retention and Distribution of Plutonium-239 in Rat Gonads.** (Eng.) Taylor, D. M. (Radiopharmacology Dept., Inst. Cancer Res., Royal

Marsden Hosp., Sutton, Surrey SM2 5PT, England) *Health Phys* 32(1): 29-31; 1977.

Data on the distribution of plutonium-239 in the rat testes and ovaries is presented. The mean uptake in the testes was 0.062 ± 0.006 (S.E.M.)% of the injected dose and that in the ovaries was 0.016 ± 0.002 (S.E.M.)% of the injected ^{239}Pu . In the rat testes about one third of the α tracks were located in the region of the spermatogonia, and a slightly greater fraction was observed above the intertubular spaces. In the ovaries the concentration of α tracks over the mature or developing follicles and the corpora lutea was only about 10% of the concentration observed over corresponding areas of stroma. ^{239}Pu was retained in the gonads over the entire period of observation. (8 refs.)

77-1447 **Influence of Trophic Level and Calcification on the Uptake of Plutonium Observed, In Situ, in Marine Organisms.** (Eng.) Guary, J. C. (International Lab. Marine Radioactivity, Musee Oceanographique, Principality of Monaco) Fraizier, A. *Health Phys* 32(1): 21-28; 1977.

Plutonium transfer mechanisms in the marine environment were studied using data on plutonium concentration factors in marine organisms. A relationship exists between the concentration of Pu in marine plant and animal species and the trophic level of these organisms. The concentration of the radioelement decreases as the trophic level of the species increases. Three modes of transport were studied: water, sediment, and food. Water was the principal mode of transfer to marine species of the lower trophic levels; sediment was not an important transfer vector. In trophic relations between animal species, Pu is transported via the food-chain. A relationship was established between the rate of Pu uptake and the calcified structures of certain marine species. (36 refs.)

77-1448 **Distribution of Plutonium-237 in a Littoral Freshwater Microcosm.** (Eng.) Trabalka, J. R. (Environmental Sciences Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) Eyman, L. D. *Health Phys* 31(4): 390-393; 1976.

A freshwater microcosm was spiked with 11 μCi of plutonium-237 nitrate to study the distribution of ^{237}Pu in this environment. The initial water concentration of ^{237}Pu was 1590 ± 86 disintegrations per min/g (dpm/g). After 90 days the surface sediment concentration was 1630 ± 282 dpm/g, the concentration of ^{237}Pu in the water was $1.8 \pm 0.9 \times 10^{-2}$ dpm/g, the distribution coefficient for sediment was 9.0×10^4 , and the trophic transfer factors were between 1.2 and 9.9% of the concentrations in the sediment. The estimated biomass concentrations of ^{237}Pu were $1 \times 10^{-1}\%$ in the water, $4 \times 10^{-2}\%$ in biota, and over 99.9% in sediments. (13 refs.)

- 77-1449 **Inhalation Studies of Condensation Aerosols Formed from PuO_2 - UO_2 Fuel and Sodium Vapor (Meeting Abstract).** (Eng.) Mahlum, D. D. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA 99352) Allen, M. D. *Radiat Res* 70(3): 638-639; 1977. (no refs.)
- 77-1450 **Biological Effects of $^{239}\text{PuO}_2$ Inhalation in the Rhesus Monkey (Meeting Abstract).** (Eng.) McClellan, R. O. (Inhalation Toxicology Res. Inst., Lovelace Res. Inst., P.O. Box 5890, Albuquerque, NM 87115) Brooks, A. L.; LaBauve, R. J.; Redman, H. C.; Mauderly, J. L.; Halliwell, W. H. *Radiat Res* 70(3): 638; 1977. (no refs.)
- 77-1451 **A Comparison of Trabecular Bone Turnover and ^{239}Pu Trabecular Surface Concentration at Five Skeletal Sites (Meeting Abstract).** (Eng.) Wronski, T. J. (Radiobiology Lab., Univ. Utah Coll. Medicine, Salt Lake City, UT 84132) Smith, J. M.; Jee, W. S. *Radiat Res* 70(3): 638; 1977. (no refs.)
- 77-1452 **Distribution of ^{239}Pu in the Gravid Baboon (Meeting Abstract).** (Eng.) Andrew, F. D. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA 99352) Bernstine, R. L.; Mahlum, D. D.; Sikov, M. R. *Radiat Res* 70(3): 637-638; 1977. (no refs.)
- 77-1453 **Cross Placental Transfer of Plutonium in Mice (Meeting Abstract).** (Eng.) Weiss, J. F. (Comparative Animal Res. Lab., Oak Ridge, TN 37830) Walburg, H. E. *Radiat Res* 70(3): 637; 1977. (no refs.)
- 77-1454 **The Distribution, Retention and Cytogenetic Effects of ^{239}Pu Citrate in the Testes of the Chinese Hamster (Meeting Abstract).** (Eng.) Brooks, A. L. (Inhalation Toxicology Res. Inst., Lovelace Res. Inst., P.O. Box 5890, Albuquerque, NM 87115) Diel, J. H.; McClellan, R. O. *Radiat Res* 70(3): 637; 1977. (no refs.)
- 77-1455 **Spatial and Temporal Distribution of PuO_2 Aerosol Particles Deposited in the Lung of a Rodent Via Inhalation (Meeting Abstract).** (Eng.) Diel, J. H. (Inhalation Toxicology Res. Inst., Lovelace Res. Inst., P.O. Box 5890, Albuquerque, NM 87115) Mewhinney, J. A.; Spines, M. B. *Radiat Res* 70(3): 684; 1977. (no refs.)
- 77-1456 **Absorbed Doses in the Marrow During ^{131}I Therapy.** (Eng.) McEwan, A. C. (Natl. Radiation Lab., Christchurch, New Zealand) *Br J Radiol* 50(593): 329-331; 1977.
- Absorbed doses to the red marrow and blood from ^{131}I therapy were reevaluated using data that have become available recently. The mean calculated marrow: blood dose ratios for thyroid cancer treatments and hyperthyroidism treatments are 0.73 and 0.70, respectively. Uncertainties in the calculations are discussed, and new dose estimates are compared with those published previously. The mean dose to the red marrow from hyperthyroidism treatment was estimated to be 0.59 rad mCi^{-1} , compared to 0.36 rad mCi^{-1} for the euthyroid state. (18 refs.)
- 77-1457 **X-Ray Induced Chromosome Aberrations in Ataxia Telangiectasia: An Indication of a Defect in DNA Repair (Meeting Abstract)?** (Eng.) Taylor, A. M. (Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham, B15 2TJ, England) Metcalf, J. A.; Oxford, J. M.; Harnden, D. G. *Mutat Res* 46(2): 161-162; 1977. (4 refs.)
- 77-1458 **Ataxia Telangiectasia. A γ -Ray Analogue of Xeroderma Pigmentosum (Meeting Abstract).** (Eng.) Paterson, M. C. (Biology and Health Physics Div., Atomic Energy Canada Ltd., Chalk River, Ontario KOJ 1J0, Canada) Smith, B. P. *Mutat Res* 46(2): 148; 1977. (no refs.)
- 77-1459 **Deficient Repair of Gamma-Damaged DNA in Xeroderma Pigmentosum Cells (Meeting Abstract).** (Eng.) Mikhelson, V. M. (Inst. Cytology, Acad. Sciences USSR, Leningrad, USSR) *Mutat Res* 46(2): 142; 1977. (2 refs.)
- 77-1460 **The Relationship Between Pathologic Ageing of the Nervous System and the DNA Repair Defects of Xeroderma Pigmentosum (Meeting Abstract).** (Eng.) Andrews, A. D. (Dermatology Branch, NCI, Bethesda, MD 20014) Barrett, S. F.; Robbins, J. H. *Mutat Res* 46(2): 105; 1977. (no refs.)

77-1461 Decreased Host-Cell Reactivation of UV-Irradiated Herpes Simplex Virus and Amount of Excision Repair in Xeroderma Pigmentosum (Meeting Abstract). (Eng.) Takebe, H. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Osaka, Japan) *Mutat Res* 46(2): 160; 1977. (no refs.)

77-1462 Decreased DNA Repair Activity and Skin Cancers in Xeroderma Pigmentosum (Meeting Abstract). (Eng.) Takebe, H. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Osaka, Japan) *Mutat Res* 46(2): 161; 1977. (no refs.)

77-1463 Correlation of DNA Strand Breakage and Repair with Survival for Low and High LET Radiation (Meeting Abstract). (Eng.) Cole, A. (Dept. Physics, Univ. Texas System Cancer Center, Houston, TX 77030) Corry, P.; Shonka, F. *Mutat Res* 46(2): 110-111; 1977. (no refs.)

77-1464 The Alkaline Elution Method and its Application to Studies of the Formation and Repair of DNA Single-Strand Breaks and Cross-Links in UV-Irradiated Human Fibroblasts (Meeting Abstract). (Eng.) Kohn, K. W. (Lab. Molecular Pharmacology, Div. Cancer Treatment, NIH, Bethesda, MD 20014) Fornace, A. J.; Ewig, R. A.; Erickson, L. C. *Mutat Res* 46(2): 131-132; 1977. (no refs.)

77-1465 Repair of DNA Breaks in Mammalian Cells Induced by Accelerated Heavy Ions (Meeting Abstract). (Eng.) Roots, R. J. (Donner Lab., Univ. California, Berkeley, CA 94720) Blakely, E. A.; Yang, T. C.; Tobias, C. A. *Radiat Res* 70(3): 685; 1977. (no refs.)

77-1466 Comparative Studies on Replicative Bypass Repair of UV Damage to DNA in Various Lines of Mammalian Cells (Meeting Abstract). (Eng.) Fujiwara, Y. (Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kobe 650, Japan) *Mutat Res* 46(2): 119-120; 1977. (no refs.)

77-1467 Potentially Lethal Damage Repair: Relationship to the Induction of Sister Chromatid Ex-

changes and DNA Repair Capacity (Meeting Abstract). (Eng.) Nagasawa, H. (Harvard Sch. Public Health, Boston, MA 02115) Fornace, A. J.; Little, J. B.; Williams, J. R. *Radiat Res* 70(3): 706; 1977. (no refs.)

77-1468 Repair of DNA Damage in Animal Cells Treated with UV or Alkylating Chemicals (Meeting Abstract). (Eng.) Ahnstrom, G. (Wallenberg Lab., Univ. Stockholm, Lilla Frescati, S-10405 Stockholm 50, Sweden) *Mutat Res* 46(2): 104; 1977. (no refs.)

77-1469 Supercoils in Nuclear DNA and the Repair of Radiation Damage (Meeting Abstract). (Eng.) Cook, P. R. (Sir William Dunn Sch. Pathology, South Parks Road, Oxford, England) Brazell, I. A. *Mutat Res* 46(2): 111-112; 1977. (no refs.)

77-1470 Kinetics of DNA Replication in Chinese Hamster Cells Following Treatment with 4,5',8-Trimethylpsoralen and Near Ultraviolet Light (Meeting Abstract). (Eng.) Meyn, R. E. (Dept. Physics, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, Texas 77030) *Mutat Res* 46(2): 140-141; 1977. (no refs.)

77-1471 Carcinogenicity of Fibrous Glass (Letter to Editor). (Eng.) Rom, W. N. (Environmental Sciences Lab., Dept. Community Medicine, Mount Sinai Sch. Medicine, New York, NY) Langer, A. M. *West J Med* 126(5): 413; 1977.

The carcinogenicity of fibrous glass, whose cancer-causing potential has been established in animal studies, is discussed. The main concern is that fine fibrous glass fibers may be inhaled, migrate to the pleura, and exert a carcinogenic effect in man exactly like asbestos. Fibrous glass may also act as a cocarcinogen with cigarette smoke and other carcinogens. That it may be biologically hazardous when inhaled is a potentially important problem that should be studied extensively. (11 refs.)

See also:

- * (Rev.): 77-1210, 77-1223, 77-1224, 77-1225, 77-1226, 77-1227, 77-1228, 77-1229.
- * (Chem.): 77-1252, 77-1357.
- * (Viral): 77-1477, 77-1526, 77-1527, 77-1543.
- * (Immun.): 77-1574, 77-1576, 77-1641.
- * (Epid.-Biom.): 77-1750, 77-1755, 77-1756, 77-1757.

VIRAL CARCINOGENESIS

7-1472 **Chromosomal Characteristics of Six Cultured Lymphoblastoid Cell Lines Originating from Marek's Disease Lymphomas.** (Eng.) Takagi, N. (Chromosome Res. Unit, Faculty Science, Hokkaido Univ., Sapporo, Hokkaido, Japan) Sasaki, M.; Ikuta, K.; Kato, S. *Biken J.* 0(1): 21-28; 1977.

Six cell lines from Marek's disease (MD) lymphomas (MOB-1, MOB-2, MOB-3, MSB-1, HPRS Line 1, HPRS Line 2) and clones (1104-B, 1104-X-5) of a cell line established from an avian lymphoid leukosis tumor were examined in light of the possible role of chromosome alteration in the etiology of MD, and also to determine distinguishing characteristics of each line. The modal chromosome number was within the diploid range in all but two lines. Grossly abnormal karyotypes were found in 4 cell lines: trisomy for #1 in MOB-2; the heteromorphic #1 pair in MSB-1, and marker chromosomes derived from rearrangements involving #3 or #5 and unidentified elements in HPRS Lines 1 and 2. The MOB-1 line was originally characterized by cells with an apparently normal karyotype; however, after 95 days of continuous growth in vitro, a consistent abnormality (a heteromorphic #1 pair morphologically similar to the one found in MSB-1) appeared. No gross chromosomal change common to all 6 MD cell lines was detected, but the possibility remains that MD virus may have caused the aberrations. The abnormal karyotypes and marker chromosomes observed in this study may be useful in distinguishing the cell lines from one another. (24 refs.)

7-1473 **DNA Polymerases of Marek's Disease Herpesvirus and Herpesvirus of Turkeys: Characterization and Mechanism of Inhibition by Phosphonoacetate (Meeting Abstract).** (Eng.) Leinbach, S. S. (Michigan State Univ., East Lansing, MI 48823) *Diss Abstr Int [B]* 37(12/Part 1): 6098; 1977. (no refs.)

7-1474 **Cell Culture Lines of JM-V Lymphoblastic Leukemia with Associated Herpesvirus (Meeting Abstract).** (Eng.) Hahn, E. C. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Ramos, L.; Kenyon, A. J. *Fed Proc* 36(3): 1085; 1977. (no refs.)

7-1475 **In Vivo Interactions Between Reticuloendotheliosis Virus Strain-T and Members of the Avian Leukemia Sarcoma Virus Group (Meeting Abstract).** (Eng.) Levine, A. S. (Indiana Univ. Sch. Medicine, Terre Haute, IN 47809) Gabbard, K. B.; Seaward, M. B.; Fung, S. *Fed Proc* 36(3): 1084; 1977. (no refs.)

77-1476 **Genetic Recombination Between Avian Leukosis and Sarcoma Viruses. Experimental Variables and the Frequencies of Recombination.** (Eng.) Blair, D. G. (Dept. Microbiology, Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033) *Virology* 77(2): 534-544; 1977.

The experimental variables affecting the recombination frequency (RF) between avian RNA tumor viruses were investigated. An infectious center assay was used to determine RF. When harvests were taken after the fourth day of double infection when a plateau in RF had been reached, different chicken embryos, the order of infection, and time of viral harvest did not influence the RF's between transformation and host range markers. Considerable variation in RF frequency was observed at earlier harvest times, with a peak occurring at 24-72 hr. Different RF's were also seen in different clones of doubly infected cells, indicating an effect of the cell on viral recombination. (31 refs.)

77-1477 **Biological and Biochemical Studies on the Inactivation of Avian Oncoviruses by Ultraviolet Irradiation.** (Eng.) Bister, K. (Dept. Microbiology, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033) Varmus, H. E.; Stavnezer, E.; Hunter, E.; Vogt, P. K. *Virology* 77(2): 689-704; 1977.

The effects of UV irradiation on the transformation and replication of avian oncoviruses and on the synthesis of virus-specific products after infection with irradiated virus were studied. The avian sarcoma viruses used were B77, Rous sarcoma viruses (RSV) of the Prague strains PR RSV-B and PR RSV-C, and RSV of the Schmidt-Ruppin strain SR-RSV-C. On the av, the 37% survival dose was 736 ergs mm⁻². The transforming capacity, as measured in the focus assay, and the sum of the replicating and transforming capacities, as measured in the infectious center assay, of B77, PR RSV-C, and PR RSV-B were inactivated at the same rate following irradiation. These assays were also performed on chicken and duck cells to measure the inactivation of B77 by UV irradiation, to determine the repair of UV damage by complementation or recombination with endogenous viruses. No repair by these methods was observed. When defective and nondefective avian sarcoma viruses were used, no significant differences in the target size of the transforming capacity of both viruses were observed. As the dose of UV irradiation increased, total virus-specific DNA synthesis decreased. DNA replication was inactivated at a lower rate than the infectivity of the virus. Both RNA synthesis and particle production decreased with increasing doses of UV irradiation, but at a lower rate than infectivity. The results confirm and extend previous investigations on the UV inactivation of avian oncoviruses. (55 refs.)

- 77-1478 Organization of Shared and Unshared Sequences in the Genomes of Chicken Endogenous and Sarcoma Viruses.** (Eng.) Neiman, P. E. (Dept. Medicine, Div. Oncology, Univ. Washington Sch. Medicine, Seattle, WA 98195) Das, S.; Macdonnell, D.; McMillin-Helsel, C. *Cell* 11(2): 321-329; 1977.

Competitive hybridization experiments indicated that the genome of Rous-associated virus type O (RAV-O) lacks about 35% of the sequences of nondefective Rous sarcoma virus (RSV) that formed hybrids with proviral DNA from RSV-infected cells. The genome of transformation-defective deletion mutants of RSV (td RSV) lacked about 15% of these sequences. Conversely, about 12% of the RAV-O sequences forming hybrids with normal chicken cell DNA were not detected in the sarcoma virus. A technique was developed to map the location of these unshared sequences by competitive hybridization. The deletion in the td RSV genome began at about 0.2 and ended at about 0.05 of the genome length from the 3' end of sarcoma virus RNA. The 35% of RSV sequences missing and/or diverged in the RAV-O genome were concentrated within 40% of the sarcoma virus genome from the 3' end; most of this large section did not appear to form hybrids with chicken DNA. A low level of hybrid formation was detected between uninfected chicken cellular DNA and a small fraction of the nucleotides in the region of the td deletion. Analysis of RAV-O 3' end fragments demonstrated that the genomic sequences of RAV-O missing in RSV were concentrated at the 3' end of the endogenous viral genome. It is concluded that sequential differences between endogenous and sarcoma viruses are largely concentrated in specific regions of the viral genome. (41 refs.)

- 77-1479 Cellular Functions are Required for the Synthesis and Integration of Avian Sarcoma Virus-Specific DNA.** (Eng.) Varmus, H. E. (Dept. Microbiology, Univ. California, San Francisco, CA 94143) Padgett, T.; Heasley, S.; Simon, G.; Bishop, J. M. *Cell* 11(2): 307-319; 1977.

The influence of the host cell on the synthesis and integration of avian sarcoma virus-specific DNA was investigated. Quail embryo fibroblasts made stationary (G₀) by serum starvation did not support the efficient synthesis of viral DNA during the first 24-48 hr after injection. The amount of DNA was diminished, particularly the amount of plus-strand DNA (identical in polarity to the viral genome), and the length of both minus and plus strands was reduced in the stationary cells. In parallel cultures fed with fresh serum, over two-thirds of the cells reentered the cell cycle within 24 hr, and normal size viral DNA was synthesized. Density labeling of viral and cellular DNA with bromodeoxyuridine was used to determine whether cellular DNA synthesis was required for integration of viral DNA. In both quail embryo fibroblasts released from G₀ and in randomly growing duck embryo fibroblasts, viral DNA was integrated only into the cellular DNA replicated during infection. The results indicated that

integration of viral DNA requires cellular DNA synthesis; this may be due to a requirement for some factor(s) present only in the S phase or to a requirement for the structural changes in cellular DNA that accompany replication. (58 refs.)

- 77-1480 Electron Microscopy of Nucleoprotein of Avian Sarcoma Virus B77 (Meeting Abstract).** (Eng.) Kanzaki, Y. (Center for Adult Diseases, Dept. Cancer Res., Kurashiki, Japan) Tanaka, T.; Oda, T. *J Electron Microscop* (Tokyo) 25(3): 185; 1976. (no refs.)

- 77-1481 In Vitro Transcription of the Total Sequences of Rous Sarcoma Virus RNA (Meeting Abstract).** (Eng.) Darlix, J. L. (Departement de Biologie Moleculaire, Universite de Geneve, CH-1211 Geneve, Switzerland) Bromley, P. A.; Spahr, P. F. *Experientia* 33(6): 816; 1977. (no refs.)

- 77-1482 Mechanism of the Rous Sarcoma Virus-Induced Decrease in the Major Cell Surface Protein of Chick Embryo Fibroblasts (Meeting Abstract).** (Eng.) Olden, K. (NIH, Bethesda, MD 20014) Yamada, K. M. *Fed Proc* 36(3): 702; 1977. (no refs.)

- 77-1483 Peptide Analyses of Envelope Glycoprotein of Rous Sarcoma Virus (Meeting Abstract).** (Eng.) Klemenz, R. (ISREC, CH-1066 Epalinges sur Lausanne, Switzerland) Diggelmann, H. *Experientia* 33(6): 822; 1977. (no refs.)

- 77-1484 Change in Leucine Amino Transferase (LAT) Isozyme Pattern During Activation of Transforming Gene in Rat Kidney Cells Transformed by Temperature Sensitive Rous Sarcoma Virus (RSV) (Meeting Abstract).** (Eng.) Roth, S. (Univ. Pennsylvania, Philadelphia, PA 19174) Delotto, R.; Kaji, A. *Fed Proc* 36(3): 738; 1977. (no refs.)

- 77-1485 Colloidal Iron Hydroxide-Binding to the Surfaces of Chick Embryo Fibroblasts Transformed by Wild-Type and a Temperature-sensitive Mutant of Rous Sarcoma Virus.** (Eng.) Subjeck, J. R. (Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263) Weiss, L.; Warren, L. *J Cell Physiol* 91(3): 329-334; 1977.

The densities of the colloidal iron hydroxide (CIH) particles

binding to the surfaces of chick embryo fibroblasts (CEF) were determined before and after transformation with wild-type Rous sarcoma virus (RSV) and a temperature-sensitive mutant (ts-RSV). At permissive and nonpermissive temperatures, the CEF were elongated and fibroblastic and they grew in regular parallel array. At 36 C both transformants showed a morphology and social behavior associated with malignancy. At 41 C the RSV- and the ts-RSV-transformed cells shed virus as at 36 C, but the ts-transformed cells no longer exhibited malignant characteristics. Particle binding in the intermicrovillous (IMV) spaces significantly increased in both RSV- and ts-RSV-transformed CEF at 36 C, compared to untransformed CEF. At 41 C a significant increase in IMV particle binding was observed in RSV-transformed cells but not in ts-RSV transformants. Following incubation with ribonuclease at 36 C, particle binding was reduced by 28% in CEF, 24% in RSV transformants, and 30% in ts-RSV transformants. At 41 C a 40% reduction was seen in both the CEF and the RSV transformant, but no change occurred in the ts-RSV transformant. Neuraminidase treatment also caused reductions in IMV particle binding in all cells at both temperatures. In vitro characteristics of normalcy and malignancy are reflected in changes in the CIH binding properties of the cell-surface IMV space. No correlations between microvilli particle density and transformation to in vitro malignant characteristics were observed. (14 refs.)

77-1486 Inhibition of the Multiplication and the Infectivity of Rous Sarcoma Virus in Chick Embryo Fibroblasts by 2-Deoxy-D-Glucose and Glucosamine (Meeting Abstract). (Eng.) Soo, W. (Lab. Chemical Biodynamics, Dept. Biochemistry, Univ. California, Berkeley, CA 94720) Bissell, M. J.; Bassham, J. A. *Fed Proc* 36(3): 741; 1977. (no refs.)

77-1487 Tumor Associated Membrane Antigens of Rous Sarcoma Virus Transformed Fibroblasts (Meeting Abstract). (Eng.) Comoglio, P. M. (Univ. Torino, 10126 Torino, Italy) Bertini, M.; Tarone, G. *Fed Proc* 36(3): 1261; 1977. (no refs.)

77-1488 A New Replication-defective Variant of the Bryan High-titer Strain Rous Sarcoma Virus. (Eng.) Murphy, H. M. (Imperial Cancer Res. Fund Labs., Post Office Box No. 123, Lincoln's Inn Fields, London, WC2A 3PX, England) *Virology* 77(2): 705-721; 1977.

Bryan high-titer Rous sarcoma virus (RSV)-transformed quail and turkey cell strains were developed that produce large quantities of cloned, defective virus particles in long-term cultures. The nonconditional, replication-defective particles from one quail cell strain (16Q) and two turkey cell

strains (α 48T and α 40T) were studied biologically and biochemically, and they were then compared with Bryan RSV strains BH-RSV(-) and α BH-RSV. The virus from the 16Q cells was of the classical Bryan type, lacking envelope glycoprotein, as shown by biological rescue and complementation studies. This virus demonstrated a higher reverse transcriptase activity and more efficient rescue and complementation than BH-RSV(-) virus. Virus particles produced by the α 40T cells were of the α BH-RSV type, lacking both envelope glycoprotein and functional reverse transcriptase. The α 48T cells produced a new replication-defective variant of the Bryan high-titer strain. Biological and complementation studies showed that this virus carries a determinant group for subgroup A envelope glycoprotein, but lacks a functional reverse transcriptase. Complementation or recombination readily occurs between the progeny of α 48T and glycoprotein-defective, virus-producing cells such as 16Q. An infectious type of RSV was recovered when two transformed cell strains, each of which was producing defective, noninfectious particles, were cocultivated. (38 refs.)

77-1489 Lack of Sequence Homology in the Two Glycoproteins, GP35 and GP85, from Rous-Associated Virus-61 (RAV-61), an Avian Retrovirus (Meeting Abstract). (Eng.) Mosser, A. G. (Biophysics Lab., Univ. Wisconsin, Madison, WI 53706) *Fed Proc* 36(3): 741; 1977. (no refs.)

77-1490 Oligo(U) as Primer for Reverse Transcriptase (Meeting Abstract). (Eng.) Palmenberg, A. (Institut für Molekularbiologie I, Universität Zürich, CH-8093 Zürich, Switzerland) Sabo, D. L.; Weissmann, C. *Experientia* 33(6): 826; 1977. (no refs.)

77-1491 Inhibition of Oncornavirus Reverse Transcriptase by β -Lapachone (Meeting Abstract). (Eng.) Schurch, A. R. (CIBA-GEIGY AG, CH 4002 Basel, Switzerland) Wehrli, W. *Experientia* 33(6): 830; 1977. (no refs.)

77-1492 The Synthesis of the Structural Proteins of Feline Leukemia Virus (Meeting Abstract). (Eng.) Okanski, G. F. (Michigan State Univ., East Lansing, MI 48823) *Diss Abstr Int [B]* 37(12/Part 1): 5983-5984; 1977. (no refs.)

77-1493 Evidence for the Replication of Bovine Leukemia Virus in the B Lymphocytes. (Eng.) Paul, P. S. (Dept. Veterinary Clinical Sciences, Coll. Veterinary

Medicine, Univ. Minnesota, St. Paul, MN 55108) Pomeroy, K. A.; Johnson, D. W.; Muscoplat, C. C.; Handwerger, B. S.; Soper, F. F.; Sorensen, D. K. *Am J Vet Res* 38(6): 873-876; 1977.

Peripheral blood lymphocytes (PBL) were taken from a cow with persistent lymphocytosis and separated on nylon wool columns into nylon-adherent and nonadherent populations. While nylon-adherent cells were highly enriched for surface immunoglobulin (SIg) bearing B lymphocytes (95.5%), nonadherent cells were enriched for SIg negative non-B cells, presumably T lymphocytes (96.3%). After 72 hr in culture, 39% of the B-enriched cells produced bovine leukemia virus as compared with 0.5% of the non-B cells, thus indicating the B lymphocytes as the major producers of bovine leukemia virus. However, when PBL and B-enriched cells were cultured with phytohemagglutinin (PHA) virus production was stimulated in both, but to a greater extent in the PBL. Since PHA is considered a T cell mitogen in the cow, it is suggested that soluble cell factors released by PHA in the B-enriched culture stimulate virus production, and that T and B cell interactions in the PBL culture are responsible for maximal virus production. (17 refs.)

77-1494 Isolation of a p15 Polypeptide from Bovine Leukemia Virus and Detection of Specific Antibodies in Leukemic Cattle. (Eng.) Kaaden, O. R. (Federal Res. Inst. Animal Virus Diseases, D-74 Tubingen, W. Germany) Frenzel, B.; Dietzschold, B.; Weiland, F.; Mussgay, M. *Virology* 77(2): 501-509; 1977.

A polypeptide (p15) isolated from bovine leukemia virus (BLV) was purified and characterized. The protein was isolated from BLV grown in the tissue culture supernatant of cultivated lymphocytes from leukemic cattle and from infected fetal lamb kidney cells. Approx 30% of the total viral BLV p15 activity was recovered in the final isolate. Upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the protein was found to be homogeneous in its electrophoretic behavior and identifiable as a single polypeptide with a molecular wt of 14,800. Double-immunodiffusion analysis of purified p15 showed that a single precipitin line formed with antisera from leukotic cattle, and a line of identity formed between antisera from animals suffering from bovine and ovine leukosis. BLV p15 failed to react with bovine syncytial virus antisera. Immunofluorescence tests detected intracytoplasmic antigens in BLV-infected cells. Absorption tests indicated that several antigens, including BLV p15, are involved in the immunofluorescence reaction. In a complement-fixation test, BLV p15 reacted only in the homologous system and with antiserum from leukotic sheep, indicating a lack of serological reactivity with the other virus antigens tested. Good correlation between the hematological status of cattle with enzootic bovine leukosis and the presence of BLV-specific precipitating antibodies was observed. (19 refs.)

77-1495 A Plaque Assay for Murine Leukemia Virus Using Enzyme-coupled Antibodies. (Eng.) Nexø, B. A. (Fibiger-Lab., 70, Ndr. Frihavnsgrde, DK-2100 Copenhagen O, Denmark) *Virology* 77(2): 849-852; 1977.

An immunoassay was developed using peroxidase-coupled antibodies that, by staining of the infected cells, allows scoring of plaques either by the naked eye or at 5- to 20-fold magnification. Cells are seeded in petri dishes in the presence of polybrene and infected the next day with a virus suspension. Three to 5 days after infection, the cultures are washed, fixed in methanol, and air-dried. The plates are incubated with antiserum to the virus and then with the peroxidase-coupled antibody. The staining mixture is added, and the plates are developed for 5-20 min at room temperature. In principle, the technique offers a plaque assay for all viruses that grow on monolayer cultures and for which an antibody is available. In practice, it has been used for the titration of xenotropic and ecotropic murine leukemia viruses. (18 refs.)

77-1496 Fractionation of Chromatin from Murine Leukemia Virus-Producing Cells (Meeting Abstract). (Eng.) MacLeod, M. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830) Reuveny, Z. *Fed Proc* 36(3): 661; 1977. (no refs.)

77-1497 Molecular Approaches to Inhibit Oncogenesis by RNA Tumor Viruses. (Eng.) Chandra, P. (Gustav-Embsden-Zentrum der Biologischen Chemie, Abteilung für Molekularbiologie, Theodor-Stern-Kai 7, Frankfurt-70, W. Germany) Ebner, U.; Steel, L. K.; Laube, H.; Gericke, D.; Mildner, B.; Bardos, T. J.; Ho, Y. K.; Gotz, A. *Ann NY Acad Sci* 284 (Part VI): 444-462; 1977.

The mode of action of inhibitors of DNA synthesis in RNA tumor viruses and the use of such inhibitors for reverse transcriptase determinations are discussed. Studies of the inhibition of the DNA polymerase of Friend murine leukemia virus (FLV) by polycytidylic acid (PC) and PC containing 5'-mercapto-substituted cytidylate units (MPC) are detailed. PC showed no activity against the viral DNA polymerase with either the endogenous viral nucleic acid or poly(rA).(dT)_n as the template. MPC samples inhibited the enzyme in direct relation to their extent of thiolation. Partially thiolated transfer RNA from Ehrlich ascites cells was a more potent enzyme inhibitor than MPC, both in the presence and absence of synthetic templates. Further experiments indicated that MPC functioned as a dead template in the viral DNA polymerase system; ie, it interacted with the enzyme but was not transcribed. Pretreatment of FLV-infected mice with MPC reduced the leukemogenic potential of cell-free spleen extracts from the mice, indicating that the polymer is a potent inhibitor of reverse transcriptase activity. Studies of the hydrolysis of MPC by micrococcal nuclease suggested that the

biological activity of 5-mercaptocytidylate units requires a large polymeric structure or that the de facto concentration decreases through the degradation of 63% of the polymer to mono- and dinucleotides. (88 refs.)

77-1498 Studies of FK-2-Mediated Resistance to Friend Leukemia Virus (Meeting Abstract). (Eng.) Blank, K. J. (Yeshiva Univ., New York, NY 10033) *Diss Abstr Int [B]* 37(12/Part 1): 5962; 1977. (no refs.)

77-1499 Role of Friend-associated Lymphatic Leukemia Virus in Immunization Against Friend Leukemia Complex. (Eng.) Bendinelli, M. (Inst. Microbiology, Univ. Pisa, via S. Zeno 39, I-56100 Pisa, Italy) *Experientia* 33(4): 455-456; 1977.

The possibility that the immunizing activity of concanavalin A (Con A) pretreated Friend leukemia complex (FLC) might be due to residual lymphatic leukemia virus (LLV) was tested. The results showed that mice inoculated with FLC pretreated with Con A are resistant to FLC challenge only when they have become infected with the FLC-associated LLV. A 100% correlation between resistance to FLC and presence of LLV in the blood of Con A-FLC injected mice at the time of challenge was observed. This demonstrated that the immunizing activity of Con A-FLC was due to residual LLV infectivity. (19 refs.)

77-1500 Translational Inhibitor from Friend Leukemia Cells (Meeting Abstract). (Eng.) Pinphanichakarn, P. (Clayton Foundation Biochemical Inst., Dept. Chemistry, The Univ. Texas, Austin, TX 78712) Kramer, G. *Fed Proc* 36(3): 868; 1977. (no refs.)

77-1501 Analysis of Peripheral Blood Lymphocytes (PBL) and Splenocytes from Mice Infected with Friend Virus (FV) (Meeting Abstract). (Eng.) Olson, G. B. (Dept. Micro., Univ. Arizona, Tucson, AZ 85721) Marie, K.; Bartels, P. H. *Fed Proc* 36(3): 1084; 1977. (no refs.)

77-1502 Evidence for Membrane-Cytoskeleton Involvement in Dimethylsulfoxide (DMSO) Induced Differentiation of Friend Leukemia Cells (FLC) (Meeting Abstract). (Eng.) Tsiftoglou, A. S. (Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT 06510) Sartorelli, A. C. *Fed Proc* 36(3): 886; 1977. (no refs.)

77-1503 Rauscher Leukemia Virus (RLV) Morphogenesis: Cleavage of P70 Can Be Accompanied by a Shift From a Helical ("Immature") to a Collapsed ("Mature") Form of the Virus Core (Meeting Abstract). (Eng.) Yoshinaka, Y. (Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545) *Fed Proc* 36(3): 740; 1977. (no refs.)

77-1504 Characterization of Intracellular Polypeptide Precursors of Reverse Transcriptase in Cells Infected with Rauscher Leukemia Virus (Meeting Abstract). (Eng.) Kopchick, J. J. (The Univ. Texas System Cancer Center M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030) Jamjoom, G. A.; Naso, R. B.; Arlinghaus, R. B. *Fed Proc* 36(3): 847; 1977. (no refs.)

77-1505 Reverse Transcription, a Probe by the Immobilized Template Poly(adenylic Acid)-Agarose. (Eng.) Milavetz, B. I. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY 14263) Horoszewicz, J. S.; Evans, M. J.; Manly, K. F.; Rinehart, K. L.; Carter, W. A. *Mol Pharmacol* 13(3): 496-503; 1977.

Poly(A)-agarose was used as an immobilized template (both primed and unprimed) to identify certain binding interactions that occur during DNA polymerization by Moloney murine leukemia virus (MoMuLV) DNA polymerase (reverse transcriptase). In addition, the effects of nucleotides and several ansamycin antibiotics on the stability of these interactions were analyzed. Detergent-disrupted MoMuLV was passed through a column containing poly(A)-agarose, the column was washed, and the polymerase activity bound was measured. Polymerization clearly required a primer, complementary nucleotides, and the presence of poly(A). Binding could not be weakened substantially by the addition of nucleotide or primer, but it could be reversed with poly(dC)•oligo-(dG)₁₂₋₁₈, which is an alternative template. Competition by poly(dC)•oligo(dG)₁₂₋₁₈ for DNA polymerase already bound to poly(A)-agarose was used to measure the effects of nucleotides. Polymerase binding to Poly(A)-agarose was markedly stabilized by the addition of primer, but complementary nucleotides destabilized the enzyme-template-primer complex significantly. The unsubstituted ansamycin streptoval C inhibited reverse transcription only when added to the polymerase-template complex, prior to primer addition. It had no ability to cause displacement of the polymerase. Rifamycin SV had a similar mode of action, although it affected other complexes to a slight degree. Demethyl-dimethylbenzyl-rifampicin inhibited the overall reaction, but it did not affect any of the complexes measured. Rifazone 8₂ was a potent inhibitor of all the complexes, especially those in which polymerase was present initially. This approach to the study of DNA polymerization may afford an alternative rationale for designing antiviral drugs. (20 refs.)

77-1506 The Subcellular Localization of Moloney Leukemia Virus (MLV) Induced Antigen(s) in the YAC Murine Cell Line (Meeting Abstract). (Eng.) Smith, C. (Dept. Biological Chemistry, Univ. Illinois Medical Center, Chicago, IL 60612) Molnar, J. *Fed Proc* 36(3): 361; 1977. (no refs.)

77-1507 In Vitro Transcription of Moloney Leukemia Virus Genes in Infected Cell Nuclei and Chromatin: Elongation of Chromatin Associated Ribonucleic Acid by *Escherichia coli* Ribonucleic Acid Polymerase. (Eng.) Shih, T. Y. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014) Young, H. A.; Parks, W. P.; Scolnick, E. M. *Biochemistry* 16(9): 1795-1801; 1977.

Viral RNA synthesis was studied in Moloney murine leukemia virus (Mo-MuLV)-infected NIH 3T3 cells in vitro. RNA synthesized in vitro by *Escherichia coli* RNA polymerase was isolated by a sulfhydryl affinity column after reaction in the presence of 5-mercuriuridine triphosphate (Hg-UTP). Comparison of the in vitro RNA with that of the 70S viral RNA showed that 1.3% in the in vitro product and 0.24% of the in vitro nuclei product contained viral sequences. Chromatin-associated RNA isolated by the same procedure except omitting the Affi-Gel purification, contained 2.5% viral sequences. This is very close to the in vivo viral RNA content of infected cells pulse-labeled with ³H-RNA. During RNA synthesis catalyzed by exogenous *E. coli* RNA polymerase in the presence of Hg-UTP, > 20% of the chromatin-associated RNA prelabeled in vivo with 5-³H-uridine was elongated and tagged with Hg atoms. The elongation reaction appeared to be due to the *E. coli* polymerase, and it was dependent on the presence of all four nucleotide triphosphates. Most of the viral-specific sequences seen in the in vitro RNA products are probably initiated and derived from the pre-existing in vivo chromatin-associated species. (38 refs.)

77-1508 Inhibitory Effect of Interferon on a Temperature-sensitive Mutant of Moloney Murine Leukemia Virus. (Eng.) Chang, E. H. (Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Disease, NIH, Bethesda, MD 20014) Myers, M. W.; Wong, P. K.; Friedman, R. M. *Virology* 77(2): 625-636; 1977.

The effects of interferon (IF) treatment on mouse thymus and bone marrow (TB) cells chronically infected with ts₁, a temperature-sensitive mutant of Moloney murine leukemia virus (MuLV), are reported. A minimum of 20 hr of exposure to IF was necessary to inhibit cell growth markedly. No significant difference in cell number was observed among cultures treated with various concentrations of IF for 26 hr. Cultures exposed to IF showed an altered pattern of virus release. Using a reverse transcriptase assay, it was discovered that there was a > 70% inhibition of virus release during the first 10

min following a drop in temperature from 39 to 34 C. The amount of extracellular virus increased tenfold between 1 and 20 min. There was a significant lag in virus release in the 20- to 30-min time period. Virus release resumed after 30 min, but it was inhibited 50%-75% compared to control. The results of varying the duration of IF suggest that IF inhibits some late stage of virus assembly. The temperature-sensitive step of virus assembly follows the IF step. The effect of IF on intracellular group-specific antigen (p30) was also studied. The level of p30 was consistently higher in cells grown at the nonpermissive temperature (39 C) than in cells grown at the permissive temperature (34 C). IF lowered the concentration of p30 in cells grown at 39 C, but it had no effect on p30 concentration in cells grown at 34 C. Analysis of virus yields by several parameters indicated that IF treatment at 39 C resulted in the release of noninfectious virus particles. (16 refs.)

77-1509 RNA Metabolism of Murine Leukemia Virus: Size Analysis of Nuclear Pulse-Labeled Virus-Specific RNA. (Eng.) Fan, H. (Tumor Virology Lab., San Inst., P.O. Box 1809, San Diego, CA 92112) *Cell* 11(2): 297-305; 1977.

A system was developed for excess DNA hybridization of Moloney murine leukemia virus (M-MuLV)-specific RNA from infected mouse cells with M-MuLV complementary DNA immobilized on nitrocellulose filters. In the presence of unlabeled heterologous rabbit liver RNA, 0.3-0.5% of labeled, infected cell nuclear RNA bound to the filters as opposed to 0.05% or less of nuclear RNA from uninfected cells. Sedimentation analysis of pulse-labeled nuclear RNA and hybridization across sucrose gradients revealed that the major pulse-labeled, virus-specific RNA was 38S, similar or identical in sedimentation to the virion subunit RNA. Although a higher molecular wt virus-specific RNA was detected, kinetic experiments showed that it was not an obligatory precursor to 38S virus-specific RNA. Simultaneous sucrose gradient analysis of steady state and pulse-labeled, virus-specific RNA showed no detectable differences between the 38S virus-specific RNA and the steady state 35S nuclear RNA previously identified. More detailed resolution on agarose gels gave similar results. Thus, the primary transcript of M-MuLV-specific RNA appears to be 38S, the same size as stable cellular virus-specific RNA. (29 refs.)

77-1510 On The Expression of Intracellular Glycoproteins Related to Murine Oncorna Viruses (Meeting Abstract). (Eng.) Rieber, M. (Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela) Bacalao, J.; Rieber, M. *Fed Proc* 36(3): 824; 1977 (no refs.)

77-1511 **A Comparison of Moloney Cell Surface and Moloney Virus Antigens (Meeting Abstract).** (Eng.) Humphrey, D. M. (Pathology Dept., Stanford Univ., Stanford, CA 94305) Witte, O. N.; Weissman, I. L. *Fed Proc* 36(3): 1261; 1977. (no refs.)

77-1512 **Genetics of Murine Sarcoma Virus (MSV)-induced Tumors in AKR Mice: Evidence That Late Progressing and Early Regressing Tumors Are Controlled by Different Genes.** (Eng.) Colombatti, A. (Lab. Experimental Oncology, Inst. Pathological Anatomy, Univ. Padua, Padua, Italy) Chieco-Bianchi, L.; De Rossi, A.; D'Andrea, E.; Collavo, D. *Int J Cancer* 19(4): 565-575; 1977.

Seventeen of 25 AKR mice injected im with a standard dose of Moloney murine sarcoma virus (M-MSV) developed progressing tumors after a mean latent period of 56 days. Studies of AKR F₁ hybrids showed that their response to M-MSV depended largely on the genetic background of the non-AKR parent. Within 4 mo of virus injection, (CBA x AKR)F₁, (DBA/2 x AKR)F₁, and (NIH x AKR)F₁ mice developed progressing tumors with a latency and growth behavior comparable to those in AKR mice. (BALB x AKR)F₁, (B6 x AKR)F₁, and (B10BR x AKR)F₁ mice did not show any late M-MSV tumors. Late tumor development was largely a function of the Fv-1 genotype, since all tumors in (B10BR x AKR) x AKR mice occurred in Fv-1-homozygous mice. The H-2k haplotype was a further factor in the development of late tumors, at least in (B6 x AKR) x AKR mice. In crosses of AKR with Fv-1-compatible mice, tumor appearance was strongly associated with the inheritance of AKR murine leukemia virus (MuLV). The MSV recovered from late tumors of first back-cross animals appeared to be a new pseudotype with the endogenous AKR-MuLV. It is suggested that the host genetic control in both early and late M-MSV tumors is exerted mainly on the helper component of the virus complex. (34 refs.)

77-1513 **Influence of Milk Source on Transplantability of Histocompatible Mammary Tumours in Mice.** (Eng.) Oth, D. (INSERM Res. Unit 95, Plateau de Brabois, 54500 Vandoeuvre, France) Sabolovic, D. *Br J Cancer* 35(6): 752-760; 1977.

The influence of milk from other mammary tumor virus (MTV)-infected mice strains on the transplantability of C3H and A.CA mammary tumors was investigated. The C3H tumors were much more easily transplantable in histocompatible recipients reared on C3H milk than recipients reared on milk from inbred Swiss/B mice. In contrast, A.CA mammary tumors grew almost equally well in histocompatible recipients reared on A.CA or Swiss/B milk. Since A.CA and C3H milks had the same effect on the transplantability of C3H tumors, the different action of Swiss/B milk on the C3H and A.CA tumors appears to be related to differences between the

two tumors or between mouse strain genotypes. The transplantability of C3H tumors changed significantly when the recipients were reared on milk from RIII mice instead of C3H. The data are discussed on the basis of a differential tolerance-inducing action of the MTVs that infect C3H, A.CA, and RIII mice. (13 refs.)

77-1514 **Propagation of Mouse Mammary Tumor Cell Lines and Production of Mouse Mammary Tumor Virus in a Serum-free Medium.** (Eng.) Bauer, R. F. (NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD 21701) Arthur, L. O.; Fine, D. L. *In Vitro* 12(8): 558-563; 1976.

A serum-free (SF) medium was developed that supports the growth of several mouse mammary tumor cell lines and the synthesis of mouse mammary tumor virus (MMTV). Eagle's minimum essential medium with Earle's balanced salts was used as the basal medium to which were added sodium bicarbonate and a serum substitute consisting of a mixture of amino acids, vitamins, inorganic salts, and buffers. Five different mouse mammary tumor cell lines were propagated in the SF medium. Growth characteristics, such as logarithmic growth, cell population increase, protein production, and days to confluency, in SF medium were comparable to those in serum-containing medium. Cells grown in SF medium could be subcultured at high split ratios and passaged continuously after adaptation to SF medium. Significantly higher levels of MMTV expression, as detected by RNA-dependent DNA polymerase assays, occurred in the SF medium subsequent to dexamethasone stimulation than in serum-containing medium. Studies involving mammary tumor cell cultures that use SF medium can provide greater standardization of culture medium by avoiding the introduction of variables and possible exogenous contaminants associated with serum. (12 refs.)

77-1515 **The Role of Leukocyte Subpopulations in the Indirect Leukocyte Adherence Inhibition Assay in the Mammary Tumor Virus System.** (Eng.) Creemers, P. (Radiobiological Inst. TNO, 151 Lange Kleiweg Rijswijk, The Netherlands) *Eur J Immunol* 7: 48-53; 1977.

A modified leukocyte adherence inhibition (LAI) test was developed to detect cellular immunologic reactivity of mice to the mammary tumor virus (MTV), which was isolated from BALB/cfC3H mammary tumors. DBA/2f mice, immunized ip with 1 µg of purified MTV, were used as positive control animals. Ten-week-old DBA/2f, BALB/c and C57BL mice served as normals. Leukocyte adherence inhibition factor (LAIF) was produced by spleen cells from immunized mice when cultured with antigen. LAIF was transferred to indicator cells for which peritoneal exudate cells from normal mice were used. In the indirect LAI assay, optimal MTV-specific LAIF production occurred after an incu-

bation period of 24 hr when a cell concentration of 20×10^6 /ml was employed. At least in the MTV system both T cells and adherent cells were necessary for producing LAIF, whose production strongly increased with prolonged incubation time. It was concluded that LAIF production occurred only when (a) adherent cells were incubated with the antigen; (b) the supernatant was transferred to T-cell-enriched cell populations; and (c) the supernatant of the latter was again transferred to adherent cells. (11 refs.)

77-1516 Embryonal Carcinoma Cells (and Their Somatic Cell Hybrids) Are Resistant to Infection by the Murine Parvovirus MVM, Which Does Infect Other Teratocarcinoma-derived Cell Lines. (Eng.) Miller, R. A. (Dept. Human Genetics, Yale Univ., New Haven, CT 06520) Ward, D. C.; Ruddle, F. H. *J Cell Physiol* 91(3): 393-401; 1977.

The interaction of minute virus of mice (MVM), a nondefective parvovirus, with (1) embryonal carcinoma cell lines, (2) other, nonpluripotent teratocarcinoma-derived cell lines, and (3) somatic cell hybrids of the embryonal carcinoma cell line PCC4azal was studied. The cells resistant to MVM were embryonal carcinoma cells PCC4azal and F9, blastocyst-derived MB2, established mouse cell lines Hepa-la and concanavalin A-stimulated splenic lymphoid cells, and the somatic cell hybrids PCT and PCF. Cells susceptible to MVM included teratocarcinoma-derived, nonpluripotent TSD4 and TS1A; blastocyst-derived MB4 and MB21; mouse embryo fibroblasts 129/Sv, C57L/J, and DBA/2J; and established mouse cell lines A9 and FBU (Friend cells). The results indicate that teratocarcinoma cultures may be useful in the study of cellular factors that mediate susceptibility to this teratogenic and oncolytic virus. (36 refs.)

77-1517 Two RNA Virus Species Synthesized by AKR Thymus Explants (Meeting Abstract). (Eng.) Stadther, J. L. (Univ. South Alabama, Mobile, AL 36617) Hughes, E. R.; Peterson, R. D. *Fed Proc* 36(3): 1084; 1977. (no refs.)

77-1518 Interspecies Homology of RNA Tumor Virus Proteins. (Eng.) Benson, J. R. (Durrum Chemical Corporation, Sunnyvale, CA 94086) Hayflick, L. *Biochemistry* 16(10): 2059-2064; 1977.

A highly sensitive column chromatographic technique was used to compare the tryptic peptide maps of RNA tumor virus proteins. Beginning with only microgram amounts of purified material, evidence of regions of relatedness was found among proteins reported to contain interspecies antigenic determinants and also in the 10,000-molecular wt proteins from feline and murine leukemia viruses. The technique combined microbore ion-exchange chromatography with a

new, highly sensitive, fluorescent assay for biogenic amines. The fluorescent assay employed o-phthalaldehyde, which in the presence of 2-mercaptoethanol reacted with primary amines to form highly fluorescent products. The discovery of coincident peptides from the 15,000- and 30,000-molecular wt proteins from murine and feline leukemia viruses supported serological evidence for interspecies antigenic determinants. The relatively large number of coeluting peptides found in the 15,000- and 10,000-molecular wt proteins is significant evidence for the existence of homology. (41 refs.)

77-1519 Mitogen Induction of Endogenous RNA Tumor Viruses (Meeting Abstract). (Eng.) Moroni, C. (Friedrich Miescher Inst. and Res. Dept., Pharmaceuticals Div., Ciba-Geigy Ltd., Basel, Switzerland) Monckton, P.; Teich, N.; Schumann, G. *Scand J Immunol* 6(6/7): 730; 1977. (no refs.)

77-1520 Increased Affinity Between Rat Embryo Non-Histone Chromosomal Proteins and Virogenic 5-Bromodeoxyuridine-Substituted DNA (Meeting Abstract). (Eng.) Schwartz, S. A. (Univ. Chicago, Chicago, IL 60637) *Fed Proc* 36(3): 1084; 1977. (no refs.)

77-1521 Amino Acid Analogs Activate Type C Viral Expression in Mouse Cells (Meeting Abstract). (Eng.) Aksamit, R. R. (NIH, Bethesda, MD 20014) Long, C. W. *Fed Proc* 36(3): 647; 1977. (no refs.)

77-1522 Virus RNA in Oncornavirus-infected Cells: 1. Characterization of Virus RNA's Associated with Cytoplasmic Particles. (Fre.) Michel, M. L. (Laboratoire d'Hematologie Experimentale, 10, Place du Docteur Fournier, Hopital Saint-Louis, 75010 Paris, France) Roussel, M.; Poitevin, E.; Samso, A.; Larsen, C. J. *Biochimie* 59(3): 275-285; 1977.

C-type particles in the cytoplasm of the Friend-virus-producing Friend-Eveline murine cell line from STU mice were observed electron microscopically and isolated by sedimentation at 90,000 g. The poly(A) RNA of the sedimentation fraction was analyzed by chromatography, gradient density, and gel electrophoresis and found to contain principally 70S and 35S RNA. Hybridization of the poly(A) RNA with complementary DNA prepared with viral RNA from Friend virus further confirmed the viral origin of the cytoplasmic particles. In order to avoid contamination of the oncornavirus particles with messenger RNA, experimental conditions were used that prevented sedimentation of the murine cell polysomes with the particles. (31 refs.)

77-1523 **Immunoperoxidase Studies of Intracytoplasmic Type A Particles in Mouse Mammary Tumor Tissue Culture Cells (Meeting Abstract).** (Eng.) Hoshino, M. Lab. Ultrastructural Res., Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya, Japan) Imai, M. *J Electron Microsc Tokyo* 25(3): 180; 1976. (no refs.)

77-1524 **Characterization of Murine Intracisternal Type A Particles (Meeting Abstract).** (Eng.) Robertson, D. L. (Washington Univ., St. Louis, MO 63130) *Diss Abstr Int [B]* 37(12/Part 1): 6105; 1977. (no refs.)

77-1525 **Ultrastructure of Human Prostatic Epithelium. Secretion Granules or Virus Particles.** (Eng.) Webber, M. M. (Div. Urology, Box C319, Univ. Colorado Medical Center, 4200 East Ninth Ave., Denver, CO 80262) Bouldin, T. R. *Invest Urol* 14(6): 482-487; 1977.

Electron microscopic observations of human prostatic tissue were conducted in an attempt to differentiate between secretion granules and virus or viruslike particles. Cytomegalovirus particles were smaller and more uniform than were secretion granules. Because the presence of virus particles in tissues is linked with the viral etiology of cancer, it is suggested that cellular particles be carefully analyzed for the structure and budding properties of oncornaviruses before being designated as "virus" or "viruslike". (15 refs.)

77-1526 **Repair of UV-Induced Alkaline Labile DNA Damage in Adenovirus after Infection of Several Human Fibroblast Lines (Meeting Abstract).** (Eng.) Rainbow, A. J. (Dept. Radiology and Dept. Biology, McMaster Univ., Hamilton, Ontario L8S 4K1, Canada) *Mutat Res* 46(2): 149-150; 1977. (no refs.)

77-1527 **Viral DNA Synthesis and Virus Production in Human KB Cells Infected with Gamma Irradiated Adenovirus (Meeting Abstract).** (Eng.) Lee, P. (Dept. Biology, McMaster Univ., Hamilton, Ontario L8S 4K1, Canada) Rainbow, A. J. *Mutat Res* 46(2): 135; 1977. (no refs.)

77-1528 **Occurrence of a Peculiar Type of Adenovirus 2 Penton Oligomer.** (Eng.) Boulanger, P. A. (Unité de Recherches No. 102 de l'Inserm, 2, Place de Verdun, F-59045 Lille Cedex, France) Puvion, F. *Intervirology* 7(3): 126-134; 1976.

Freshly purified penton preparations of adenovirus type 2 were found to contain a preferential species, as well as a ringed structure resembling that observed in adenovirus types 3 and 4 hemagglutinin preparations. Ultracentrifugation showed two components, a major one sedimenting at 10.5S, and a minor one at 29.4S. Electrophoretic analysis revealed that the major band corresponded to isolated pentons and that the minor band corresponded to penton oligomers. Electron micrographs confirmed the tetrameric structure of these penton oligomers. (27 refs.)

77-1529 **Role of Ad-2 Virus DNA Synthesis in the Production of Virion Antigens.** (Eng.) Polasa, H. (Dept. Microbiology, Osmania Univ., Hyderabad-7, India) *Indian J Med Res* 64(9): 1342-1346; 1976.

The role of viral DNA synthesis in adenovirus type 2 (Ad-2) capsid protein production was studied in infected KB cells. Fluorodeoxyuridine was used as an inhibitor of DNA synthesis. DNA synthesis was found essential for the production of virion antigens and virus. The results also indicated that progeny viral DNA code for these antigens. (21 refs.)

77-1530 **Specific Interaction of a Protein(s) at or Near the Termini of Adenovirus 2 DNA (Meeting Abstract).** (Eng.) Padmanabhan, R. (Dept. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63110) Padmanabhan, V.; Byrnes, B. W. *Fed Proc* 36(3): 740; 1977. (no refs.)

77-1531 **Electron-Microscopy of Replicating Adenovirus-2 DNA Molecules (Meeting Abstract).** (Eng.) Lechner, R. (Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Kelly, T. J. *Fed Proc* 36(3): 655; 1977. (no refs.)

77-1532 **Physical Properties of Nucleoprotein Cores from Adenovirus Type 5.** (Eng.) Harpst, J. A. (Dept. Biochemistry, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH 44106) Ennever, J. F.; Russell, W. C. *Nucleic Acids Res* 4(2): 477-490; 1977.

Results of characterization of nucleoprotein core complexes from type 5 adenovirus, consistent with previous findings, showed that the cores are complexes of DNA and identifiable viral proteins. Sedimentation results confirmed the conclusion that the core polypeptides markedly condense the viral DNA. Thermal denaturation showed that the internal polypeptides stabilize the secondary structure of DNA. The separate effects of the two core polypeptides on the structure and

stability of the DNA and on the biological functions of the virus remain to be defined. (35 refs.)

- 77-1533 **Freeze-Etching Observation on the Nucleus of HeLa-S3 Cell Infected with Adenovirus Type 12.** (Eng.) Fujio, K. (Dept. Virology, Okayama Univ. Medical Sch., Okayama, 700 Japan) Ichikawa, K.; Kumon, H.; Uno, F.; Tawara, J. *J Electron Microsc* 25(4): 297-298; 1976.

The fine structure of the adenovirus crystal arrangement in the nucleus was demonstrated by freeze-etching. There were approx 500 adenovirus particles in the crystal. The virions were hexagonal, with an av diameter of 80 nanometers. When the inner components of the virion were removed by cutting, the inner smooth surface of the capsid could be observed. The internal core was a knoblike particle in the center of the virion, and it also had a smooth surface. The capsomeres appeared as small granules, but it was difficult to distinguish penton from hexon. The interaction of the core and capsomere and of the virus cell were clearly demonstrated. Freeze-etching methods are concluded to be suitable for observing the processes of virus maturation in the nucleus and cytoplasm. (4 refs.)

- 77-1534 **Identification of an Immunologically Distinct Papillomavirus from Lesions of Epidermodysplasia Verruciformis (Meeting Abstract).** (Eng.) Pass, F. (Univ. Minnesota Medical Sch., Minneapolis, MN 55455) Reissig, M.; Shah, K. V.; Eisinger, M.; Orth, G. *Fed Proc* 36(3): 1084; 1977. (no refs.)

- 77-1535 **Branching Pathways in Cleavage Processing of Picornaviral Proteins (Meeting Abstract).** (Eng.) Matthews, T. J. (Univ. Wisconsin, Madison, WI 53706) Omilianowski, D. R.; Rueckert, R. R. *Fed Proc* 36(3): 919; 1977. (no refs.)

- 77-1536 **Surface Features of Human Fibroblasts Infected by Vaccinia Virus (Meeting Abstract).** (Eng.) Gamliel, H. (Hebrew Univ.-Hadassah Medical Sch. and Hadassah Univ. Hosp., Jerusalem, Israel) Polliack, A.; Sarov, I. *Isr J Med Sci* 13(6): 640-641; 1977. (no refs.)

- 77-1537 **The Relation of Viral Hepatitis to Primary Hepatic Carcinoma (Meeting Abstract).** (Eng.) Karasawa, T. (Dept. Pathology, Univ. Tokyo Sch. Medicine, Tokyo, Japan) Shikata, T. *Gastroenterol Jpn* 12(1): 84; 1977. (no refs.)

- 77-1538 **Studies on the Progression of Viral Hepatitis to Primary Hepatoma with Special Reference to Hepatitis B Virus (Meeting Abstract).** (Eng.) Kiyosawa, K. (Dept. Internal Medicine, Faculty Medicine, Shinshu Univ., Matsumoto, Japan) Koike, Y. *Gastroenterol Jpn* 12(1): 82-83; 1977. (no refs.)

- 77-1539 **Antibody to Hepatitis B Core Antigen in Patients with Hepatocellular Carcinoma.** (Eng.) Kubo, Y. (Second Dept. Medicine, Kurume Univ. Sch. Medicine, Kurume, Japan) Okuda, K.; Hashimoto, M.; Nagasaka, Y.; Ebata, H.; Nakajima, Y.; Musha, H.; Sakuma, K.; Oh-take, H. *Gastroenterology* 72(6): 1217-1220; 1977.

Hepatitis B surface antigen (HBsAg), anti-HBs, and anti-HB core (HBc) were measured in 124 patients with hepatocellular carcinoma (HCC), 299 control subjects of comparable ages, in 48 patients with chronic hepatitis, and in 52 patients with hepatic cirrhosis. In the HCC group, 72.6% of patients were positive for anti-HBc, as compared to 30.1% in the controls. More than 80% of HCC patients reacted positively to at least one of the antigens tested, a percentage significantly greater ($p < 0.01$) than that found in the control group (34.1%). Thus, the majority of HCC patients had evidence for hepatitis B virus infection in the past or present. (33 refs.)

- 77-1540 **Neutralizing EBV-Specific IgA in Throat Washings of Nasopharyngeal Carcinoma (NPC) Patients.** (Eng.) Desgranges, C. (Unit Biological Carcinogenesis, International Agency for Res. on Cancer, Lyons, France) de-The, G.; Ho, J. H.; Ellouz, R. *Int J Cancer* 19(5): 627-633; 1977.

Throat washings from 26 nasopharyngeal carcinoma (NPC) patients from Hong Kong and Tunisia were examined for the presence of transforming Epstein-Barr virus (EBV). Only six (23%) were found positive, possibly due to a neutralizing factor in such salivas. The search for EBV-specific antibodies showed that NPC saliva contained neutralizing viral capsid antigen (VCA) and early antigen (EA) IgA (54% and 27% respectively) and VCA and EA IgG (73% and 54% respectively). Electron microscopy revealed virus particles in both transforming and nontransforming throat washings, but in nontransforming salivas (containing IgA and IgG) the particles were clumped. Comparative study of throat washings from patients with Burkitt's lymphoma, infectious mononucleosis, immunodeficiencies, other cancers, and healthy subjects showed that IgA were restricted to NPC cases. (30 refs.)

- 77-1541 **The Establishment and Cytological, Cytochemical and Immunological Characterization of Human Haemic Cell Lines: Evidence for Heterogeneity.** (Eng.)

arpas, A. (Dept. Haematological Medicine, Cambridge Univ. Clinical Sch., Cambridge, England) Hayhoe, F. G.; Greenberger, J. S.; Barker, C. R.; Cawley, J. C.; Lowenthal, J. M.; Moloney, W. C. *Leukemia Res* 1(1): 35-49; 1977.

Continuous tissue culture lines were established from the bone marrow or peripheral blood of 18 patients with acute myeloid leukemia (AML) and 10 patients with lymphoid leukemia. The morphological and immunological properties of these cell lines were studied after 6 mo-2 yr growth in liquid culture. All lines tested except a single T-cell line were positive for Epstein-Barr virus nuclear antigen. All but the T-cell line and two others showed cell-surface characteristics similar to those of the blastoid lines of lymphoid origin. Thirteen of the 28 cell lines revealed positivity for alkaline phosphatase, which is not normally found in lymphoid precursors, and most showed some positivity to α -naphthol AS-D acetate esterase and chloroacetate esterase at near neutral pH but not to α -naphthyl butyrate or chloroacetate at pH 8. Only 5/24 lines tested for lysozyme production were positive, all of them from patients with AML. All 10 lines derived from patients with myeloid leukemias were positive for phagocytic activity; none of the three lines from patients with nonmyeloid leukemias showed phagocytosis. There were no outstanding differences in the pattern of surface immunoglobulin expression between the lines derived from patients with myeloid or lymphoid malignancies. (39 refs.)

77-1542 **Prospective Study of Epstein-Barr Virus Antibody Titre and Survival in Patients with Nasopharyngeal Carcinoma (Letter to Editor).** (Eng.) Chan, S. H. (Dept. Pathology, Faculty Medicine, Univ. Singapore, Singapore 3) De The, G.; Goh, E. H. *Lancet* 1(8018): 948-949; 1977.

Antibodies to Epstein-Barr virus (EBV)-related antigens were measured in 119 newly diagnosed nasopharyngeal carcinoma patients. Antibody titers against early antigen (EA), virus capsid antigen (VCA), and nuclear antigen (EBNA) were determined. Patients were treated with radiotherapy and followed up for > 2 yr. Patients with lower titers survived longer than those with higher titers. EA titer had the best prognostic value, but EBNA did not prove to be very useful. The results indicate that EBV-related antibodies may be useful in the prognosis and management of patients with nasopharyngeal carcinoma. (4 refs.)

77-1543 **Epstein-Barr Virus (EBV) Antibody in Patients Treated by Radical Radiotherapy for a Head and Neck Cancer (Meeting Abstract).** (Eng.) Halili, M. R. (Dept. Radiology, Section Radiotherapy, Albert Einstein Coll. Medicine, Bronx, NY) Spigland, I.; Foster, N.; Ghossein, N. A. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 86; 1976. (no refs.)

77-1544 **Effects of Herpes Simplex Virus (HSV) on Human and Murine Lymphocyte Cultures (Meeting Abstract).** (Eng.) Kirchner, H. (German Cancer Res. Center, Inst. Immunology, Heidelberg, W. Germany) Schwentek, M. *Fed Proc* 36(3): 1228; 1977. (no refs.)

77-1545 **Tryptic Fingerprint Analysis of Herpes Simplex Virus Nucleocapsid Proteins (Meeting Abstract).** (Eng.) Cohen, G. H. (ISREC, CH-1066 Epalinges sur Lausanne, Switzerland) Diggelmann, H. *Experientia* 33(6): 816; 1977. (no refs.)

77-1546 **Simulation of α , β and Herpes Simplex Virus-Induced DNA Polymerases by DNA Binding Proteins (Meeting Abstract).** (Eng.) Blue, W. (Roche Inst. Molecular Biology, Nutley, NJ 07110) Weissbach, A. *Fed Proc* 36(3): 734; 1977. (no refs.)

77-1547 **A Type Specific Antibody Induced by a Major Herpesvirus Type 1 Glycoprotein (Meeting Abstract).** (Eng.) Ching, C. Y. (Sloan-Kettering Inst. Cancer Res., New York, NY 10021) Lopez, C. *Fed Proc* 36(3): 1076; 1977. (no refs.)

77-1548 **Replication of Type I Herpes Simplex Virus (HSV) in Primary Cultures of Hairy Cell Leukemic Leukocytes (Meeting Abstract).** (Eng.) Pozner, L. H. (Duke Univ. Medical Center, and VA Hosp., Durham, NC 27710) Cohen, H. J.; Logue, G. L.; Croker, B. P.; Cooper, J. A.; Daniels, C. A. *Fed Proc* 36(3): 1085; 1977. (no refs.)

77-1549 **Growth of Herpes Simplex Virus (HSV) Type II in Human Mononuclear Leukocytes from Umbilical Cord Blood (Meeting Abstract).** (Eng.) Trofater, K. F. (Williams, R. J.) Gall, S. A.; Daniels, C. A. *Fed Proc* 36(3): 1076; 1977. (no refs.)

77-1550 **Effect of Hormones on Herpes Simplex Virus Type-2-Induced Transformation.** (Eng.) Gupta, P. (Dept. Microbiology, Milton S. Hershey Medical Centre, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033) Rapp, F. *Nature* 267(5608): 254-255; 1977.

The effect of different hormones on herpes simplex virus type 2 (HSV-2) was studied. A rapid quantitative assay for trans-

formation by HSV-2 using a thymidine kinase (TK) selection procedure was used. Transformation of a TK- mouse cell line by HSV-2 was carried out in the presence of cortisol, estradiol-17 β , or dexamethasone. Transformation was inhibited by cortisol (10^{-5} to 10^{-7} M) and estradiol (10^{-5} M), but dexamethasone (10^{-5} to 10^{-7} M) had little effect. Inhibition was not due to toxic effects on the host cells, and it was still observed when the hormones were added 6-7 hr after the virus. It was concluded that the inhibition of transformation by hormones is probably not due to the failure of adsorption, penetration, or uncoating of the infecting virus particles. The mechanism by which hormones might inhibit integration of viral genes into the cellular genome is unknown. (9 refs.)

- 77-1551 **Immunomodulator-induced Resistance Against Herpes Simplex Virus.** (Eng.) Morahan, P. S. (Dept. Microbiology, Box 847, Medical Coll. Virginia, Richmond, VA 23298) Kern, E. R.; Glasgow, L. A. *Proc Soc Exp Biol Med* 154(4): 615-620; 1977.

The antiviral activities of three immunomodulators, *Corynebacterium parvum*, *C. acnes*, and pyran, were compared. Treatment with pyran, but not with corynebacteria, increased the survival time of adult Swiss mice after intravaginal infection with herpes simplex virus type 2 (HSV-2). All three immunomodulators, however, protected mice from mortality following ip infection with HSV-2. Eight-day-old suckling mice were treated ip with pyran or levamisole and infected ip with HSV-2 24 hr later. Levamisole had no protective effect on the course of the disease. Treatment with pyran produced a slight reduction in mortality from 100% in controls to 75%, and it prolonged the survival time from 6.0 days to 9.8 days. Treatment of 8-day-old mice with levamisole and/or *C. acnes* had no protective effect on the course of disease in mice infected 14 days later with HSV-2. Silica treatment, which increased the susceptibility of mice to virus infection 10 to 100 times, suppressed macrophage function. Silica treatment did not inhibit the antiviral activity of *C. acnes* or pyran, and the increased susceptibility induced by silica was associated with early viral replication. (23 refs.)

- 77-1552 **Expression of Herpesvirus Genome in Cells Derived from Bone Marrow of Latently Infected Guinea Pigs (Meeting Abstract).** (Eng.) Gonzalez-Serva, A (VA Hosp., West Haven, CT 06516) Hsiung, G. D. *Fed Proc* 36(3): 1076; 1977. (no refs.)

- 77-1553 **The Presence of *Herpesvirus saimiri* Genomes in Virus-Transformed Cells.** (Eng.) Fleckenstein, B. (New England Regional Primate Res. Center, Harvard Medical Sch., 1 Pine Hill Drive, Southborough, MA

01772) Muller, I.; Werner, J. *Int J Cancer* 19(4): 546-554; 1977.

Herpesvirus saimiri-transformed cells were found to contain both forms of viral DNA, unique L-DNA and repetitive H-DNA. Cotton-top marmoset monkeys were inoculated in with *H. saimiri* strain S295C. After 4-5 wk, palpable inguinal and axillary lymph nodes were detected as signs of progressing malignant lymphoma. The animals were killed and autopsied. At autopsy, DNA from the spleen and lymph nodes was found to contain 0.14%-0.75% viral L-DNA and 0.115%-1.08% H-DNA. The H-DNA was equivalent to 14-130 M genomes per diploid tumor tissue cell. Virus-producing lymphoid cell lines established in vitro from the lymph nodes of *H. saimiri*-infected marmosets contained 1.19%-1.24% L-DNA and 1.67%-1.91% H-DNA. This amount of H-DNA was equivalent to 202-230 M genomes per cell. *H. saimiri* transformed non-virus-producing lymphoid cell lines contained 0.72%-1.75% L-DNA and 0.69%-1.75% H-DNA. The H-DNA content of these cells was equal to 83-274 M genomes per cell. In the nonproducer lymphoid cell lines part of the L-sequences present in the virions were found to be deleted in the genome copies of transformed cells, indicating a defect in the viral genome. These results contribute to the general view that cells transformed by oncogenic herpesviruses contain a relatively high concentration of persisting viral DNA sequences with high genetic complexity. (33 refs.)

- 77-1554 **Lymphoma in Cotton-top Marmosets after Inoculation with Epstein-Barr Virus: Tumor Incidence, Histologic Spectrum Antibody Responses, Demonstration of Viral DNA, and Characterization of Viruses** (Eng.) Miller, G. (Dept. Pediatrics, Yale Univ., Sch. Medicine, New Haven, CT 06510) Shope, T.; Coope, D.; Waters, L.; Pagano, J.; Bornkamm, G. W. *Henle, W.* 145(4): 948-967; 1977.

The results of inoculations of cotton-top marmosets with Epstein-Barr virus (EBV) are presented, and the spectrum of histologic responses is delineated. A total of 6/20 cotton-top tamarins inoculated with EBV developed diffuse malignant lymphoma resembling reticulum cell or immunoblastic sarcoma of man. In eight animals, inapparent infection with development of antibody was noted. EB nuclear antigen was observed in imprints of two lymph nodes, one with hyperplasia and one with lymphoma. EBV DNA was detected in cell lines from two lymphomas and in the tumors of three animals. The malignant lymphoma seemed to arise from a cell with an uncleaved vesicular nucleus in the center of the germinal follicle. Elaboration of the cytoplasmic membrane with microvilli and significant formation of rough endoplasmic reticulum were found. The absence of membrane receptors for the Fc fragment of immunoglobulin G or complement on transformed cells and the elevated production of virus by transformed cells are factors involved in the increased tumorigenicity of EBV in the marmoset. (28 refs.)

77-1555 **Nucleic Acid Sequences of Primate Type C Viruses in Normal and Neoplastic Human Tissues.** (Eng.) Prochownik, E. V. (Dept. Pathology, Univ. Chicago, Chicago, IL 60637) Kirsten, W. H. *Nature* 267(5607): 175-177; 1977.

Molecular hybridization techniques were used to demonstrate that HEL-12 cells (normal human embryonic lung fibroblasts) contain proviral DNA sequences before antigen expression or virus release can be detected and that the DNA's from certain cancer patients contain nucleic acid sequences homologous to HEL-12 viral RNA. DNA was extracted from early-passage HEL-12 cells in which C-type viral antigens were not detected or from late-passage HEL-12 cells that spontaneously released C-type virus. The DNA was heated, denatured and reannealed in the presence of trace amounts of ¹²⁵I-HEL-12 viral RNA. Both early- and late-passage cells contained DNA sequences homologous to HEL-12 viral RNA. DNA sequences hybridizable to the RNA of HEL-12 virus were also found in DNA samples from the spleen of an 11-yr old boy with osteogenic sarcoma and from the spleen of an adult with acute myelogenous leukemia. (1 refs.)

77-1556 **Elevated Expression of T-Antigen in Skin Fibroblasts from Individuals with Cytogenetic Abnormalities Infected In Vitro with Simian or Human Papovaviruses.** (Eng.) Lubiniecki, A. S. (Life Sciences Div., Celco Labs., Inc., 6715 Electronic Drive, Springfield, VA 22151) Costa, J.; Rabson, A. S. *Proc Soc Exp Biol Med* 505: 507; 1977.

The question whether a human papovavirus might exhibit elevated T-antigen expression in skin fibroblasts from high-cancer-risk groups [as is the case with fibroblasts from these groups infected in vitro with simian papovavirus 40 (SV40)] was investigated. Human skin fibroblasts from normal individuals and from patients suffering from Fanconi's anemia, Turner's syndrome, and Klinefelter's syndrome were infected with human papovavirus (BK type) or SV40 at multiplicities of infection that induced similar frequencies of T-antigen-containing cells 72 hr after infection. Indirect immunofluorescent assays for T antigen were performed using hamster sera raised against SV40 T antigen. For both viruses, the four normal cell strains expressed T antigen less frequently than the strains from the three clinical groups at high cancer risk. These results also permitted analysis of the relative infectivity of SV40 and BK papovavirus. It was estimated that BK papovavirus is 20 times more infectious for human cells than is SV40, which is consistent with qualitative evidence of the host cell preferences of these viruses. (23 refs.)

77-1557 **Characterization of SA12 as a New Oncogenic SV40-Related Papovavirus (Meeting Abstract).** (Eng.) Valis, J. D. (Johns Hopkins Univ., Baltimore, MD

21205) Newell, N.; Reissig, M.; Malherbe, H.; Shah, K. V. *Fed Proc* 36(3): 1085; 1977. (no refs.)

77-1558 **Growth Factor Requirement of SV40-Virus Transformed 3T3 (SV3T3) Cells (Meeting Abstract).** (Eng.) Paul, D. (The Salk Inst., Box 1809, San Diego, CA 92112) *Fed Proc* 36(3): 925; 1977. (no refs.)

77-1559 **Variation in the Appearance of SV40 Tumor Antigen in Transformed Cells.** (Eng.) Robb, J. A. (Dept. Pathology, Univ. California, San Diego, La Jolla, CA 92093) *Exp Cell Res* 106(2): 441-445; 1977.

Five types of variation in the appearance of SV40 T antigen were identified by immunofluorescence in wild-type and tsD* 101 transformed BALB and Swiss/3T3 cells. While some clones had more than 95% uniformly stained nuclei, others had variable stained nuclei. Nuclei were T-negative at the periphery at 39 C, but not at 33 C in some clones; the reverse held true in D101 cells having T-negative nuclei at 39 C, but not at 33 C, during growth and after saturation. Finally, wild-type cells had T-negative nuclei after confluence at both 33 and 39 C. This fifth type of variation may involve an immunospecificity change in the T antigen molecule. It is concluded that any models proposed for the regulation of SV40 T antigen in transformed cells will have to explain these variations. (21 refs.)

77-1560 **SV40 Specific Cell Surface Antigens Have Resulted in Selection of Tumorigenic Cells Which are Revertants for the Expression of SV40 Early Genes (Meeting Abstract).** (Eng.) McFarland, V. W. (NIH, Bethesda, MD 20014) Chang, C.; Kuster, J. M.; Mora, P. T. *Fed Proc* 36(3): 741; 1977. (no refs.)

77-1561 **DNA Polymerases Bound to Replicating SV40 Chromosomes (Meeting Abstract).** (Eng.) Waqar, M. A. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY 14263) Huberman, J. A.; Evans, M. J. *Fed Proc* 36(3): 654; 1977. (no refs.)

77-1562 **Primary Structure At and Near the Origin of DNA Replication in Simian Virus 40 (Meeting Abstract).** (Eng.) Subramanian, K. N. (Univ. Illinois Medical Center, Chicago, IL 60612) Weissman, S. M. *Fed Proc* 36(3): 654; 1977. (no refs.)

- 77-1563 Expression of the SV40-Transformed Phenotype in Hybrids Between Conditional and Wild-type Transformants.** (Eng.) Rovigatti, U. (Cattedra di Biologia Molecolare, Istituto di Fisiologia Generale, Universit di Roma, Rome, Italy) Basilico, C. *Exp Cell Res* 106(2): 277-284; 1977.

Two different SV40-transformed cell lines that are temperature sensitive (ts) for the expression of the transformed phenotype were analyzed by somatic cell hybridization. When ts 23A cells, temperature sensitive in their ability to grow in medium containing low serum, and a standard SV40-transformed BALB/c 3T3 cell line, were hybridized, the mutation appeared to be dominant, at least for some parameters. All of the hybrid clones had a very low efficiency of plating in medium containing 1% serum, but only 50% of them showed growth inhibition in mass culture under the same conditions. Ts H615 cells reverted to a normal phenotype at 39 C for most parameters of transformation, whereas the hybrids generally behaved like transformed cells at this temperature, suggesting that the ts H615 mutation is recessive. However, the expression of this mutation was not completely suppressed, since DNA synthesis after confluence showed some degree of inhibition in the hybrids at 39 C. The considerable variation observed in the behavior of individual hybrid clones and in the degree of inhibition of some parameters is discussed in terms of possible mechanism(s) of transformation. (30 refs.)

- 77-1564 Strandedness of Newly Synthesized Short Pieces of Polyoma DNA from Isolated Nuclei.** (Eng.) Flory, P. J. (Dept. Biochemistry, Medical Nobel Inst., Karolinska Inst., 104 01 Stockholm, Sweden) *Nucleic Acids Res* 4(5): 1449-1464; 1977.

Hybridization was used to compare the extent of discontinuous synthesis of the two complementary strands of polyoma DNA at each growing fork during DNA synthesis in isolated nuclei. The kinetics of self-annealing of short pieces of labeled DNA were examined before and after a second Sepharose 4B chromatography and alkaline hydrolysis step. After the final purification, 95% of the label hybridized to polyoma DNA, but the max extent of self-annealing was 75%. This result indicates that there are differences in the amount of short pieces synthesized from the E (early RNA synthesis) and L (late RNA synthesis) strands. Next, the amounts of the newly synthesized strands arising from different portions of the genome were determined by separately mixing them with an excess of each of the sonicated HpaII restriction fragments 1-4, denaturing, and annealing. The fraction of shortpiece label annealed as a function of time was analyzed by hydroxypapatite chromatography. More E than L strand short pieces annealed to fragments 2 and 4, but the reverse was true for fragments 1 and 3. During replication, the E strand of fragments 2 and 4 and the L strand of fragments 1 and 3 grow in the 3'5' direction and are therefore expected to be synthesized discontinuously. The results indicated that in every case

there was a 1.4- to 2.4-fold excess of short pieces from the strand growing in the 3'5' direction. (17 refs.)

- 77-1565 In Vitro Transcription of Polyoma Virus DNA.** (Eng.) Yaniv, M. (Departement de Biologie moleculaire, Institut Pasteur, Paris, France) Cremisi, C. Croissant, O.; Oudet, P.; Pignatti, P. F.; Lescure, B. In: *In Vitro Transcription and Translation of Viral Genomes. Proceedings of a Conference held in Paris-Grignon, 15-18 Ju 1975*. INSERM, EMBO, DGRST. (Paris, France): vol. 4 pp. 83-91; 1975.

Polyoma virus was studied to show the existence of promoter sites on viral DNA and to examine binding sites for *Escherichia coli* RNA polymerase and eukaryotic RNA polymerase B. Two HindII cleavage sites and one BamI cleavage site were located at positions 0.26, 0.36 and 0.50 respectively, on the physical map of the polyoma (PY) virus genome. Cleavage of PY DNA-bacteriophage T4 gene 3 protein complexes with either Eco-RI or BamI showed that the adenine- and thymine-rich regions that bind this protein are located at 0.25 and 0.8. Alkaline denaturation of Eco-RI linear PY DNA provided additional information on the distribution of the A-T rich regions on the DNA molecule. Initiation sites for *E. coli* and calf thymus RNA polymerase B on superhelical DNA or on linear DNA were located on the physical map by either electron microscopy or hybridization. *E. coli* RNA polymerase was able to recognize sites on both superhelical and linear DNA. T superhelical DNA contained two- to threefold more enzyme molecules than the linear DNA. Calf thymus RNA polymerase B also showed recognition for sites on both templates and exhibited a fivefold increase in affinity for the superhelical DNA. Strong *E. coli* polymerase binding sites corresponded to positions of low frequency binding of calf thymus RNA polymerase B, and vice versa. The bound enzyme molecules on linear DNA could be located relative to the nearest end in agreement with sites located on superhelical DNA. Both polymerases may have a similar mechanism of template recognition requiring an A-T rich region, a partial unwinding of the double helical structure, and a specific base sequence for strong binding and initiation. These experiments suggest that the eukaryotic enzyme recognizes specific sequences on the viral DNA. (2 refs.)

- 77-1566 Polyoma-Induced Stimulation of Cellular RNA Synthesis is Paralleled by Changed Expression of the Viral Genome.** (Eng.) Salomon, C. (Dept. Molecular Biology, Univ. Geneva, 1211 Geneva 4, Switzerland) Turler, H.; Weil, R. *Nucleic Acids Res* 4(5): 1483-1503; 1977.

The synthesis of viral and cellular RNA was studied in confluent, primary mouse kidney cell culture during lytic infection with polyoma virus at either 27 C or 37 C. When 5-fluorodeoxyuridine (FdU), an inhibitor of DNA synthesis,

as added to infected cultures, expression of the early viral gene took place: early 19S polyoma messenger RNA (mRNA) and polyoma tumor (T)-antigen were synthesized. An immediate mitogenic reaction of the host cell led to an increase of $30 \pm 5\%$ in cellular, mainly 28S and 18S rRNA, followed by activation of the cellular DNA-synthesizing apparatus. Polyoma-induced cellular RNA synthesis, with increased production of early 19S mRNA, led to subsequent expression of the late viral genes and to synthesis of small amounts of late 19S and 16S mRNAs. Changed expression of the viral genome occurred in the absence of detectable synthesis of polyoma DNA I. Infection in the absence of FdU induced the same sequence of events, followed, however, by replication of the mouse cell chromatin (S-phase) and production of progeny virus. (39 refs.)

77-1567 **Polyoma Virus-Specific RNA in Cytoplasm and Detergent-Washed Nuclei of Productively-Infected Mouse Cells (Meeting Abstract).** (Eng.) Montanari, P. E. (ISREC, CH-1066 Epalinges sur Lausanne, Switzerland) Acheson, N. H. *Experientia* 33(6): 825; 1977. (2 refs.)

77-1568 **Complementation Between Temperature-sensitive (ts) and Host Range Nontransforming (hr-t) Mutants of Polyoma Virus.** (Eng.) Eckhart, W. (Salk Inst., Post Office Box 1809, San Diego, CA 92112) *Virology* 72(2): 589-597; 1977.

The results of experiments testing the complementation between polyoma temperature-sensitive (ts) and host-range-nontransforming (hr-t) mutants are reported. Tests of complementation in lytic infection using mouse 3T3 cells showed that hr-t mutants supply the early tsA function required for viral DNA synthesis at the nonpermissive temperature (39°C) and the virion protein required for infectious progeny virus production by the late mutants at this temperature. Experiments measuring complementation for transformation (by mixed infection of hamster BHK or rat Y1 cells) showed that six different tsA-type mutants can complement for transformation with the hr-t mutant. No complementation was observed in pairwise crosses among the early tsA-type mutants alone. The tsA-type mutants are situated in the distal portion of the early region of the polyoma genome, and the hr-t mutants are located in the proximal portion. These findings suggest that the early region of the polyoma genome consists of two functional regions that can complement for transformation. (29 refs.)

77-1569 **Hr-t and ts-a: Two Early Gene Functions of Polyoma Virus.** (Eng.) Fluck, M. M. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115) Staneloni, R. J.; Benjamin, T. L. *Virology* 77(2): 610-624; 1977.

The divergence in phenotypes of "early" temperature-sensitive (ts-a) and single complementation (hr-t) mutants is further characterized. Both of these polyoma virus mutants have lost the ability to transform cells, and the mutations are found in the early region of the viral DNA. They were compared in detail using virus-cell and virus-to-virus complementation tests, spot tests, and gene-dosage experiments. The growth of the ts-a mutants did not respond to the host factors of Py-3T3, ts-a-3T3, NIH-sTs(MLV), or UCI-B in the same manner as the hr-t mutants. The ts-a group showed a low degree of leakiness (0.01%-1%), the magnitude of which was characteristic of the individual mutant. The leakiness of the hr-t mutants was rarely $< 1\%$. Complementation between the hr-t NG-18 mutants and the ts-a ts-25D mutant was most efficient at an input ratio of ts-25D to NG-18 $> 50:1$. Under optimal conditions, complementation between NG-18 and mutants of early and late ts classes is both symmetric and efficient. This suggests that each mutant class represents a gene coding for a diffusible product carrying out different functions in the virus growth cycle. Gene-dosage experiments indicated a catalytic role for the ts-a wild-type product and a partial dominant lethal effect of hr-t mutant products. Hr-t and ts-a viral genes control different stages in the processes of viral growth and cell transformation. (47 refs.)

77-1570 **Host Range Selection of Transformation-defective hr-t Mutants of Polyoma Virus.** (Eng.) Staneloni, R. J. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115) Fluck, M. M.; Benjamin, T. L. *Virology* 77(2): 598-609; 1977.

Using host-range selection with polyoma-transformed 3T3 cells as the permissive host and normal 3T3 cells as a nonpermissive host, 19 independent mutants were isolated. All 19 failed to transform rat and hamster fibroblasts. Experiments indicated that these 19 mutants belong to a single complementation group, designated hr-t, which signifies defects in host range and transformation. Virus-induced cell killing, the appearance of both early and late viral antigens, and the final low yields of infectious virus are evidence of an intracellular block in the developmental cycle of this class of mutant. Small deletions in the DNA's were present in some of the mutants, notably in the proximal (5') part of the early region. All mutants isolated by this procedure showed a uniform biological behavior, which suggested that the reduced host range and the inability to induce cell transformation are due to a single mutation. A model for the alteration of the expression of cellular genes by the hr-t viral mutant is presented. (28 refs.)

77-1571 **Correlation Between Genetic Loci and Structural Differences in the Capsid Proteins of Polyoma Virus Plaque Morphology Mutants.** (Eng.) Hewick, R. M. (Dept. Protein Chemistry, Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Fields, London WC2A

3PX, England) Waterfield, M. D.; Miller, L. K.; Fried, M. *Cell* 11(2): 331-338; 1977.

Two plaque morphology variants (A-2 and 208) of polyoma virus (PV) showed marked differences in agarose gel electrophoresis of the whole particles, isoelectric focusing of the major capsid protein VP1 (45,000 daltons), and three tryptic peptides (A, B, and C) of VP1. Correlations were made between phenotype, portions of the primary amino acid sequence of VP1, and the physical map of PV DNA by analysis of the capsid protein from large plaque A-2 virus, minute plaque 208 virus, and large plaque 208 virus selected after marker rescue with a fragment of PV DNA generated by the Hpa II restriction enzyme. All five marker rescued isolates selected for large plaque morphology showed only two A-2 specific properties, the absence of peptide C in tryptic maps of VP1, and the aggregation of VP1 on isoelectric focusing, while the other four properties that distinguish A-2 and 208 were present or absent in 40%-60% of the isolates. Three of the four A-2 specific properties (presence of peptide A, absence of peptide B, and isoelectric point of VP1) occurred coordinately in the marker rescued isolates. The fourth property (electrophoretic mobility of virus particles in agarose gels) segregated independently. (14 refs.)

77-1572 In Vitro Transformation of Hamster Brain Cells by Polyoma Virus. (Fre.) Pagis-de Micco, C. (Unité 119 de l'I.N.S.E.R.M., Faculté de Médecine de Marseille, 27, boulevard Jean-Moulin, 13385 Marseille Cedex 4, France) Tripier, M. F.; Hassoun, J.; Toga, M. *C R Acad Sci [D] (Paris)* 284(13): 1231-1234; 1977.

Cultured cells from the cerebral cortex of the Syrian hamster were transformed 90-120 days after infection with the "small plaque" mutant of polyoma virus obtained from mouse embryo cultures. Dissociated fragments of hamster cerebral cortex from 24-hr-old animals were trypsinized and suspended in PUC N 16 medium with added fetal calf serum, glucose, and glutamine and maintained at 37 C in 5% carbon dioxide atmosphere. The brain cells were inoculated with 500 plaque forming units of virus per cell, and viral contact was maintained for 3 hr at 37 C under continuous agitation. Cells were then washed and resuspended, and the culture medium was renewed twice a week. Transformation was evident 90-120 days after infection, when the rate of growth increased rapidly. Changes in cell morphology were observed by phase contrast, light, and electron microscopy. Subcutaneous injection of 5×10^6 cells from the 18th passage induced tumors, palpable about 20-30 days after injection, in newborn hamsters. The tumors could be transplanted serially in adult animals, and they produced pulmonary metastases as well as locally invasive malignancies. The polyoma virus T antigen was found on 5%-10% of the transformed cells, and the virus membrane S antigen was found on 75%-90%. The transformed cells are presently in their 46th passage and have been designated the HC x Py cell line. (10 refs.)

See also:

- * (Rev.): 77-1232, 77-1233, 77-1234, 77-1235, 77-1236
- * (Chem.): 77-1282, 77-1371.
- * (Phys.): 77-1461.
- * (Immun.): 77-1573, 77-1574, 77-1581, 77-1582, 77-1590, 77-1594, 77-1628, 77-1642, 77-1648, 77-1671, 77-1675, 77-1682, 77-1683, 77-1686.
- * (Path.): 77-1704, 77-1712, 77-1726.
- * (Epid.-Biom.): 77-1760.

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- 77-1573 Identification of a Cell-Surface Antigen Selectively Expressed on the Natural Killer Cell.** (Eng.) Glimcher, L. (Dept. Medicine, Harvard Medical Sch., Farber Cancer Center, Boston, MA 02115) Shen, F. W.; Cantor, H. *J Exp Med* 145(1): 1-9; 1977.

The serologic definition of a cell surface component which is selectively expressed on the surface of natural killer (NK) cells active against a MuLV+ tumor is described. The NK cells did not express Thyl, Ly2, or Ig surface markers, but did express an antigen recognized by C3H anti-CE antiserum (anti-Ly1.2 antiserum). This antiserum, termed anti-NK, defines a new subclass of lymphocytes which may play a role in immunosurveillance against tumors. (22 refs.)

- 77-1574 Generation of Natural Killer Cells: An Autonomous Function of the Bone Marrow.** (Eng.) Haller, O. (Dept. Immunology, Uppsala Univ. Biomedical Center, Uppsala, Sweden) Kiessling, R.; Orn, A.; Wigzell, H. *J Exp Med* 145(5): 1411-1416; 1977.

The generation of natural killer (NK) cells in spleens from radiation chimeras produced between pairs of histocompatible highly- and poorly-NK-reactive mouse strains was examined. Radiation chimeras were produced after lethal irradiation (800 R) of 8- to 10-wk-old animals by bone marrow exchange between the two H-2b-compatible strains C57L (high) and A.BY (low). Bone marrow reconstitution (iv inoculation of 3×10^7 cells from sex-matched donors) restored NK activity in the spleens and rendered the chimeras highly or poorly reactive in complete accordance with the NK characteristics of the bone marrow donor strain, independent of the host environment. Spleen cells from B10.A-A/J chimeras had a higher killing capacity for YAC-1 than cells from A/J-A/J mice. Spleen cells of poorly-reactive mice grafted with bone marrow or fetal liver cells from high donors were highly reactive, while spleen cells of highly-reactive recipients reconstituted with bone marrow from poorly-reactive mice were poorly reactive. The age-related changes of NK activity were expressed at the level of the bone marrow precursor cell. The generation of NK cells does not depend on the genotype or other influences of the host environment and is an inborn and autonomous function of the bone marrow. (8 refs.)

- 77-1575 Presence of Natural Killer Cell Activity in Cytotoxic Lymphocytes from MLC-CML Reactions (Meeting Abstract).** (Eng.) Ortaldo, J. R. (LID, NCI, NIH, Bethesda, MD 20014) Bonnard, G. D. *Fed Proc* 36(3): 1325; 1977. (no refs.)

- 77-1576 Suppression of Natural Killer Cell Activity with Radioactive Strontium: Effector Cells Are Marrow Dependent.** (Eng.) Haller, O. (Dept. Immunology, Biomedical Center, Uppsala Univ., Uppsala, Sweden) Wigzell, H. *J Immunol* 118(4): 1503-1506; 1977.

To determine the bone marrow dependence of natural killer (NK) cell function, inbred CBA mice and (CBA \times C57BL6) F_1 hybrids (F_1 mice) known to exert high NK activity were treated twice with ^{90}Sr (100 μCi ip). The mice were sacrificed 6 wk later, and their spleens were harvested and checked for in vitro NK activity and antibody-dependent cell-mediated cytotoxicity (ADCC) to chick RBC. Spleen cells from five untreated low-responder (A \times ASW) F_1 mice were also included. NK activity against YAC-1 tumor cells (from a Moloney virus-induced lymphoma) was determined. Control spleen cells from ^{90}Sr -untreated CBA and F_1 mice were highly active, and as expected, cells from the lower responders showed low activity. However, the lowest killing capacity was found with cells from ^{90}Sr -treated CBA mice. The decrease in cytotoxicity was statistically significant at all three effector-to-target cell ratios tested. ^{90}Sr also reduced the NK activity in the spleens of the F_1 mice. When spleen cells from CBA and F_1 mice were tested for ADCC reactivity, ^{90}Sr did not abrogate killing against chick RBC. The effect of ^{90}Sr was also investigated on the in vivo induction of cytolytic T lymphocytes. ^{90}Sr -treated and untreated CBA and F_1 mice were immunized ip with P-815 ascites mastocytoma cells. The spleen cells from all immunized mice showed lytic ability, and, in both mouse groups, the differences in immune spleen cell cytotoxicity against P-815 between ^{90}Sr -treated and untreated animals were not statistically significant. The results indicate that, in vivo, a functional bone marrow is needed to generate and maintain NK activity. (20 refs.)

- 77-1577 Macrophages and Neoplasia.** (Eng.) Mansell, P. W. In: *Immunocancerology in Solid Tumors*. Martin, M.; Dionne, L., eds. (Miami: Symposia Specialists): pp. 51-61; 1976.

When 4 mg of the β 1-3-glucopyranose polysaccharide Glucan (a powerful reticuloendothelial system stimulator) were given simultaneously with 20×10^6 Shay tumor cells sc to rats, there was a significant inhibition of tumor growth. Within the first 12 hr after injection, the number of macrophages in the tumor increased 70%. Rats were also given 5×10^6 tumor cells iv and, on days 1-5, 0.2 mg Glucan iv or glucose controls. Both groups developed the leukemic phase that characterized the tumor, but the treated group recovered while the controls died of disseminated disease. A total of 20×10^6 Shay tumor cells was mixed with peritoneal exudate cells (PEC) obtained

4 days after the administration of 10 ml of a 0.5% suspension of Glucan ip. Tumor and PEC cells were given sc simultaneously in ratios of 10:1, 2:1, and 1:1. Tumor growth was inhibited significantly, especially when the ratio was 1:1. In the controls, heavy infiltration of the liver and spleen with tumor was found, and few host cells were seen in the local tumor. In the treated groups, there was a significant decrease in infiltration, and large numbers of macrophages were present. In the 1:1 ratio group, very few tumor cells were observed in the liver, and those that were present were about to be destroyed by monocytic cells. In final experiments, animals that had survived tumor implantation with Glucan were challenged 30 days later with 30×10^6 Shay tumor cells sc, and the tumors were weighed on the 11th day. The av wt of the tumor in the control animals was 18.3 g, but the wt of the tumor in the immune animals was 0.7 g. Histologically, the tumor in the immune animal was composed of fibrous tissue with macrophages. In clinical trials, of the tumor nodules injected with humoral recognition factor (HRF) alone, 70% demonstrated necrosis 48 hr after injection. In those patients who were given either HRF with Glucan or Glucan alone, the necrosis was more obvious and occurred in 100% of the treated lesions. The mechanism of action of HRF seems to be one of complexing with the tumor cell. (33 refs.)

77-1578 Characterization of Surface Proteins of Macrophages (Meeting Abstract). (Eng.) Remold-O'Donnell, E. (Center for Blood Res., Boston, MA 02115) *Fed Proc* 36(3): 1252; 1977. (no refs.)

77-1579 Analysis of Macrophage Mediated Cytostasis (Meeting Abstract). (Eng.) Pasternack, G. R. (Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205) Shin, H. S. *Fed Proc* 36(3): 1263; 1977. (no refs.)

77-1580 Functional Heterogeneity in the Mouse Macrophage Cell Line IC-21 (Meeting Abstract). (Eng.) Serio, C. S. (Div. Immunology, St. Jude Children's Res. Hosp., Memphis, TN 38101) Walker, W. S. *Fed Proc* 36(3): 1263; 1977. (no refs.)

77-1581 Replication of HSV-1 in Macrophages from Resistant and Susceptible Mice (Meeting Abstract). (Eng.) Lopez, C. (Sloan-Kettering Inst., New York, NY 10021) Dudas, G. J. *Fed Proc* 36(3): 1076; 1977. (no refs.)

77-1582 Induction of Cell Mediated Cytotoxicity by Macrophages (Meeting Abstract). (Eng.) Schmidtke, J. R. (Univ. Minnesota, Minneapolis, MN 55455) *Fed Proc* 36(3): 1280; 1977. (no refs.)

77-1583 Lymphoid Compartmentalization of Immunoregulatory Activity (Meeting Abstract) (Eng.) Schwartz, S. A. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021) Choi, Y. S.; Good, R. A. *Fed Proc* 36(3): 1210; 1977. (no refs.)

77-1584 Inhibition of Tumor Cell Migration In Vitro (Meeting Abstract). (Eng.) Cohen, M. C. (Dept. Pathology, Univ. Connecticut Health Center, Farmington CT 06032) Yoshida, T. *Fed Proc* 36(3): 1299; 1977. (no refs.)

77-1585 Generation of ^{125}I UdR-Labeled Specifically Cytotoxic T Lymphocytes for Use in Tumor Homing Studies (Meeting Abstract). (Eng.) Hansen, C. B. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Russell, W. *Fed Proc* 36(3): 1293; 1977. (no refs.)

77-1586 Mechanism of Target Cell Lysis by Cytolytic T Lymphocytes. I. Characterization of Specific Lymphocyte-Target Cell Conjugates Separated by Velocity Sedimentation. (Eng.) Ryser, J. E. (Dept. Immunology, Swiss Inst. Experimental Cancer Res., CH-1066 Epalinges-sur-Lausanne, Switzerland) Sordat, B.; Cerottini, J. C.; Brunner, K. T. *Eur J Immunol* 7(2): 110-117; 1977.

Conjugates of immune lymphoid cells and target cells (TC) were separated from free lymphocytes by differential velocity sedimentation when small-sized lymphocytes and large-sized TC were used. P-815 mastocytoma cells maintained by serial passage in syngeneic DBA/2 mice were used for immunization, and cultures of these cells were used as TC for conjugate formation and for the cytolytic assay. Cytolytic T lymphocytes were obtained from C57BL/6 mice inoculated ip with 3×10^7 P-815 cells. The mice were sacrificed 10-11 days later, and peritoneal cells were collected. Small peritoneal lymphocytes (SPL) were isolated from the alloimmune peritoneal cell population, and the large tumor cells were selected as TC. Most of the conjugates formed at room temperature consisted of one SPL bound to one TC, and bound SPL could be separated from free SPL within < 5 min. In the conjugate-enriched fractions, at least 60% of the TC-bound SPL were cytolytic. However, fractions depleted of conjugates still exhibited up to one-third of the original lytic activity, suggesting that not all effector cells formed stable conjugates at room temperature. Transmission and scanning electron microscopy revealed that SPL and TC were bound by interpenetrating membrane projections characterized by point and broad zone contacts. When lysis was permitted to proceed, the morphology of the TC membrane changed prominently; ie, microvillous projections and were replaced by localized blebs, pseudopod-type projections, and membrane defects. (29 refs.)

77-1587 Characterization of Human Lymphocyte Subpopulations for Cytotoxicity Against Tumor-derived Monolayer Cultures. (Eng.) Bakacs, T. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden) Gergely, P.; Cornain, S.; Klein, E. *Int J Cancer* 19(4): 441-449; 1977.

Lymphocyte fractions of three healthy donors were tested in a 48-hr assay for cytotoxicity against cell lines derived from two osteogenic sarcomas, a nasopharyngeal carcinoma, and a mammary carcinoma. Analysis of surface markers indicated that a non-T, non-B fraction comprising about 50% of Fc receptor-positive cells had the strongest cytotoxic activity. The cell yield in this fraction averaged 6.5% of the nonfractionated population. Elimination of cells positive for surface immunoglobulins did not influence the cytotoxic effect. Pure T cells, isolated by early antigen (EA)-rosette formation subsequent to passage on nylon wool columns, had no or very low cytotoxicity. Null cells, ie, cells without detectable surface markers and present in the fraction containing the Fc-positive cells, were also cytotoxic. The results confirm that T cells are not responsible for the natural cytotoxicity of human blood lymphocytes. (25 refs.)

77-1588 Differential Growth of Allogeneic Lymphocytes and Bone Marrow Cells in Irradiated NZB Mice (Meeting Abstract). (Eng.) Eastcott, J. W. (Boston Univ. Sch. Medicine, Boston, MA 02118) Bennett, M.; Munn, C.; Broitman, S. A. *Fed Proc* 36(3): 1225; 1977. (no refs.)

77-1589 Suppression of Lymphocyte Proliferation by a Non-specific Factor Produced by the Daudi Lymphoblast Cell Line (Meeting Abstract). (Eng.) Poulik, M. D. (William Beaumont Hosp., Royal Oak, MI 48072) Lightbody, J. *Fed Proc* 36(3): 1237; 1977. (no refs.)

77-1590 Lymphocyte Populations of *Callithrix jacchus* (CJ) Marmosets (Meeting Abstract). (Eng.) Wright, R. (Univ. Illinois Medical Centers, Chicago, IL 60612) Wright, J.; Falk, L. A.; Wolfe, L. G.; Deinhardt, F. *Fed Proc* 36(3): 1240; 1977. (no refs.)

77-1591 Anomalous Capping Behavior of Chronic Lymphocytic Leukemia (CLL) Lymphocytes Despite Normal Antibody Binding and Tubulin Levels (Meeting Abstract). (Eng.) Liebes, L. (N.Y.U. Sch. Medicine, New York, NY 10016) Fleit, H.; Ambady, S.; Quagliata, F.; Silber, R. *Fed Proc* 36(3): 711; 1977. (no refs.)

77-1592 Lymphocyte Activating Factor Production by Mouse Tumor Cell Lines in Culture (Meeting Abstract). (Eng.) Hacker, M. P. (Yale Univ. Sch. Medicine, New Haven, CT 06510) Lachman, L.; Blyden, G. T.; Hand-schumacher, R. E. *Fed Proc* 36(3): 1300; 1977. (no refs.)

77-1593 In Vitro Lymphocyte Activity in Tumor-Bearing Mice (Meeting Abstract). (Eng.) Kapoor, Q. S. (Dept. Physiology and Biophysics, Univ. Oklahoma Health Sciences Center, Oklahoma City, OK, 73190) Chowdhury, T. K. *Fed Proc* 36(3): 1258; 1977. (no refs.)

77-1594 In Vitro Sensitization of Human Peripheral Blood Lymphocytes to Autologous Lymphoid Cell Lines: Influence of B-Cell (Ia), Epstein-Barr Virus (EBV), and Fetal Calf Serum (FCS) Antigens (Meeting Abstract). (Eng.) Spina, C. A. (UCLA, Sch. Medicine, Los Angeles, CA 90024) Fahey, J. L. *Fed Proc* 36(3): 1249; 1977. (no refs.)

77-1595 T Cell Regulation of Null Cell Function In Vivo (Meeting Abstract). (Eng.) Reinisch, C. L. (Sidney Farber Cancer Inst., Div. Tumor Immunology, Boston, MA 02115) O'Connell, K. *Fed Proc* 36(3): 1322; 1977. (no refs.)

77-1596 Multiple Occurrence of Spontaneous AKR/J Lymphomas with T and B Cell Characteristics. (Eng.) Greenberg, R. S. (Dept. Infectious Diseases, Massachusetts General Hosp., Boston, MA 02214) Mathieson, B. J.; Campbell, P. S.; Zatz, M. M. *J Immunol* 118(4): 1181-1190; 1977.

The existence of three Thy 1.1-positive, immunoglobulin-positive (Thy 1+, SIg+) AKR/J lymphomas is documented. Two of the tumors (AkTB-1 and AkTB-2) originated as spontaneously occurring lymphomas in the peripheral lymphoid tissues of 14- and 16-mo-old AKR/J male mice thymectomized at 1 mo of age. AkTB-3 originated in a 16-mo-old AKR/J mouse that had an atrophic thymus at necropsy. As determined by multiple criteria, including immunofluorescence, all three have endogenous T- and B-cell markers, ie, Thy 1.1, Ly, easily detectable SIg, Fc receptor (FcR), and immune response region antigen (Ia). The persistence of Thy 1.1 antigen and SIg after long-term tissue culture showed that these markers were not acquired passively. AkTB-1 lymphoma always grows in lymph nodes as Thy 1+, SIg- cells; in the spleen, however, the cells are initially Thy 1+, SIg-, but they rapidly acquire SIg, FcR, and Ia between 18 and 21 days of passage. As these cells multiply in the spleen, they

may crowd out suppressive T cells, thereby permitting expression of SIg. The consistent occurrence of doubly marked AKR lymphomas in old mice with atrophic or absent thymuses suggests a systematic difference in leukemogenesis between these mice and younger ones with intact thymuses, in which tumors are classically Thy 1+, SIg- (52 refs.)

77-1597 Characterization of Precursor B Cells in Human Bone Marrow (Meeting Abstract). (Eng.)

Okos, A. J. (Dept. Pediatrics, Univ. Alabama in Birmingham, Birmingham, AL 35294) Gathings, W. E. *Fed Proc* 36(3): 1294; 1977. (no refs.)

77-1598 Evidence for a Surface Receptor for Human Migration Inhibitory Factor on a B-Lymphoid Cell Line (Meeting Abstract). (Eng.)

McLeod, T. F. (Univ. Miami Sch. Medicine, Miami, Florida 33152) Cordeiro, P. G.; Glade, P. R. *Fed Proc* 36(3): 1299; 1977. (no refs.)

77-1599 Histamine Receptor Display on Lymphocyte Subpopulations (Meeting Abstract). (Eng.)

Roszkowski, W. (Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21239) Plaut, M.; Lichtenstein, L. M. *Fed Proc* 36(3): 1241; 1977. (no refs.)

77-1600 Membrane Receptors of Lymphoreticular Cells in Hyperplastic and Neoplastic Diseases of the Lymphatic System. (Ger.)

Kruger, G. (Immunpathologische Laboratorien, Pathologisches Institut, Universität zu Köln, Köln, W. Germany) Uhlmann, C.; Hellriegel, K. P.; Sesterhenn, K.; Samii, H.; Fischer, R.; Wustrow, F.; Gross, R. *Haematol Bluttransfus* 18: 17-31; 1976.

B and T cell receptors were determined in 105 patients with lymphoreticular and lymphoepithelial neoplasia and compared to similar investigations of 582 cases reported in the literature, in 35 healthy individuals, 12 normal lymph nodes, hyperplastic conditions of lymph nodes from 30 patients, and the tonsils of 85 patients. The cells were characterized by immunofluorescence and monospecific anti-immunoglobulin antisera, anti-thymus antiserum, and E-rosettes. While normal blood and normal and hyperplastic tissues showed a polyclonal distribution of proliferation of lymphoreticular cells, neoplastic conditions often had exuberant, possibly monoclonal proliferation. B cell neoplasias consisted of the chronic lymphocytic leukemias, well differentiated lymphocytic lymphomas, Burkitt's tumor, follicular lymphoma Brillsymmers, and hairy cell leukemia. T cell lymphomas comprised a large part of poorly or undifferentiated leukemias of children, poorly differentiated lymphocytic lymphomas, prolym-

phocytic leukemia, and Sezary's syndrome. Monocytic neoplasias were malignant histiocytoses and leukemic reticuloendothelioses. There were tumors lacking both B and T cells Hodgkin's lymphomas, mycosis fungoides, and histiocytic lymphomas. The prognostic and pathogenetic implications of the combined morphological and immunological classification of lymphoreticular neoplasias are discussed. (27 refs.)

77-1601 Studies on Capping of Lymphocyte Complement Receptors (Meeting Abstract). (Eng.)

Gormus, B. J. (Minneapolis V. A. Hosp. Minneapolis, MN 55417) Basara, M.; Kaplan, M. E. *Fed Proc* 36(3): 1235; 1977. (no refs.)

77-1602 The Binding of Functional C1 on Normal and Various Malignant Cells (Meeting Abstract)

(Eng.) Teshima, H. (Sloan-Kettering Inst. Cancer Res., New York, NY 10021) Kitamura, H.; Day, N. K. *Fed Proc* 36(3): 1282; 1977. (no refs.)

77-1603 Lymphocyte Bound Fourth Component of Complement (C4) in a Patient Lacking Serum C4 (Meeting Abstract). (Eng.)

Jackson, C. G. (Univ. Washington, Sch. Medicine, Seattle WA 98195) Ochs, H. D. *Fed Proc* 36(3): 1208; 1977. (no refs.)

77-1604 Development of a Culture System for Transitional Epithelial Cells Which Synthesize the First Component of Complement (C1) (Meeting Abstract)

(Eng.) Morris, K. M. (Center for Blood Research, Boston MA 02115) *Fed Proc* 36(3): 1209; 1977. (no refs.)

77-1605 Isolation and Characterization of the FC Receptors of the Murine Leukemia L1210 (Meeting Abstract). (Eng.)

Cooper, S. M. (USC School Medicine, Los Angeles, CA 90033) Sambray, Y. *Fed Proc* 36(3): 1186; 1977. (no refs.)

77-1606 Isolation and Characterization of Fc Surface Receptors for Human IgE from Cultured Human Lymphoblastoid Cells (Meeting Abstract). (Eng.)

Meinke, G. C. (Scripps Clinic, Res. Foundation, La Jolla, CA 92037) Spiegelberg, H. L. *Fed Proc* 36(3): 1186; 1977. (no refs.)

77-1607 Two Distinct (Fc) Receptors for IgG on a Mouse Cell Line (Meeting Abstract). (Eng.) Anderson, C. L. (Natl. Jewish Hosp. and Res. Center, Denver, CO 80206) Heusser, C. H.; Grey, H. M. *Fed Proc* 36(3): 1252; 1977. (no refs.)

77-1608 Interaction of Isolated Variable and Constant Domains of Light Chain with Heavy Chain of Immunoglobulin G (Meeting Abstract). (Eng.) Klein, M. (Dept. Biochemistry, Univ. Toronto, Toronto, Canada M5S 1A8) Kortan, C.; Alexander, I.; Kells, D. I.; Dorrington, K. I. *Fed Proc* 36(3): 1198; 1977. (no refs.)

77-1609 Prevention of IgG₂a Production as a Result of Allotype-Specific Interaction Between T and B Cells. (Eng.) Bosma, M. J. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111) Bosma, G. C. *J Exp Med* 145(3): 743-748; 1977.

It was shown that cytotoxic or suppressor T cells specific for the IgG₂a allotype of C57BL mice (G²) were able to prevent the growth of a cogenic G²-producing plasmacytoma. This was interpreted as direct evidence for allotype-specific interaction between T and B lymphocytes. The significance of such cell-to-cell interactions for IgG regulation is discussed. (21 refs.)

77-1610 Characterization of the IgG₂a Immunoglobulin Synthesized by a Secondary Variant of the IgG₂ Producing Cell Line of the Mouse Myeloma Tumor, NPC 1 (Meeting Abstract). (Eng.) Francus, T. (Dept. Cell Biology, Albert Einstein Coll. Medicine, Bronx, NY 10461) Birshen, B. K. *Fed Proc* 36(3): 1309; 1977. (no refs.)

77-1611 Comparative Studies on Monotypic IgM Lambda and IgG Kappa from an Individual Patient--II. The Complete Amino Acid Sequence of the VH Region of the IgM Paraprotein. (Eng.) Capra, J. D. (Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Dallas, TX) Hopper, J. E. *Immunochemistry* 13(12): 995-999; 1976.

The complete amino acid sequence of the variable region of the heavy chain (VH) of an immunoglobulin M (IgM) lambda paraprotein was determined, and it was compared to the sequences of nine published human VH-III myeloma proteins. This paraprotein is one of a pair (the other being IgG3 kappa) obtained from a single individual's sera that have been shown to have highly similar, if not identical, idiotype determinants. In the second hypervariable region, there are two unusual substitutions: valine and threonine rather than the usual alanine-proline are in positions 41 and 42. No deviations

from the alanine-proline sequence had been seen previously in human VH III myeloma proteins. A deletion at position 60 had also not been found previously in human VH III myeloma proteins. The chain also contains an exceptionally long fourth hypervariable region. The variability illustrated by this protein is similar to that of the nine previously sequenced proteins. (22 refs.)

77-1612 An Altered IgM Phenotype in an Adapted Line of Mouse Plasmacytoma Cells (Meeting Abstract). (Eng.) Marks, R. (Inst. Cancer Res., Fox Chase, Philadelphia, PA 19111) Hausman, S. J.; Bosma, M. J. *Fed Proc* 36(3): 1199; 1977. (no refs.)

77-1613 IgE Mediated Histamine and Serotonin Release from Cultured Mouse Mastocytoma Cells (Meeting Abstract). (Eng.) Taurog, J. D. (NIAMDD and NIDR, NIH, Bethesda, MD 20014) Hook, W. A.; Siragani-an, R. P.; Metzger, H. *Fed Proc* 36(3): 1215; 1977. (no refs.)

77-1614 Antisera to Rat Basophilic Leukemia Cells and the Receptor for IgE (Meeting Abstract). (Eng.) Conrad, D. H. (MRC Group, Dept. Immunology, Univ. Manitoba, Winnipeg, Manitoba, R3E 0W3.) Yiu, S. H.; Froese, A. *Fed Proc* 36(3): 1217; 1977. (no refs.)

77-1615 Excessive IgA Production by Lymphocytes from Patients with the Sezary Syndrome and Low Numbers of Circulating Neoplastic T-Cells (Meeting Abstract). (Eng.) Broder, S. (Metabolism Branch, NCI, NIH, Bethesda, MD 20014) Dobbins, W. O.; Waldmann, T. A. *Fed Proc* 36(3): 1210; 1977. (no refs.)

77-1616 Suppression of Eosinophil (EOS) Chemotaxis by IgA Paraproteins (Meeting Abstract). (Eng.) Reed, K. (Univ. New Mexico, Albuquerque, NM 87106) Epps, D. V.; Williams, R. *Fed Proc* 36(3): 1212; 1977. (no refs.)

77-1617 Mouse T-Cell Tumour Immunoglobulin. I. Antigenic Properties and Effects on T-Cell Responses. (Eng.) Boylston, A. W. (Dept. Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England) Watson, S. R.; Anderson, R. I. *Immunology* 31(5): 827-835; 1976.

The immunochemical properties and effects on T-cell func-

tions were investigated for an immunoglobulin (designated TCT Ig) produced by the mouse tissue cultured T-cell tumors El-4 and WEHI-22. The active factor is a mouse Ig, because it can be absorbed with insoluble antibodies that react with mouse kappa chains and this absorption can be blocked by preincubating the immunosorbent with pure mouse IgG. The TCT Ig appears to belong to a new class of mouse Ig, because its effects on in vitro antibody responses cannot be absorbed with antisera to any of the known classes of mouse Ig. The active agent in TCT Ig does not react with antibody directed toward the histocompatibility antigens of the cells producing it. TCT Ig affects only T-cell functions directly concerned in antibody responses. It acts only on those steps in cooperative antibody responses that lie between the ability of the T cell to respond to antigen and the ability of the B cell to produce antibody. It has no effect on the ability of the different subclasses of T cells to respond to mitogens or to alloantigens. These findings suggest that the molecular basis for T-T cooperation differs from that of T-B cooperation. (26 refs.)

77-1618 Murine T Cell Lymphoma Immunoglobulin (Meeting Abstract). (Eng.) Moseley, J. M. (Walter and Eliza Hall Inst. Medical Res., Melbourne, Australia) Marchalonis, J. J. *Fed Proc* 36(3): 1185; 1977. (no refs.)

77-1619 Detection of Intracellular Immunoglobulins in Non-Hodgkin's Lymphomas (Meeting Abstract). (Eng.) Davey, F. R. (SUNY Upstate Medical Center, Syracuse, NY 13210) Halliday, D.; Marucci, A. A.; Gottlieb, A. J. *Fed Proc* 36(3): 1240; 1977. (no refs.)

77-1620 Lymphocyte Surface Immunoglobulin (SIG) Density and In Vitro Immunoglobulin (IG) Secretion in Chronic Lymphocytic Leukemia (CLL) (Meeting Abstract). (Eng.) Chen, Y. H. (VA West Side Hosp. and Univ. IL Abraham Lincoln School of Medicine, Chicago, IL) Heller, P. *Fed Proc* 36(3): 1326; 1977. (no refs.)

77-1621 Primary Structure of a Bence-Jones Cryoprotein (Meeting Abstract). (Eng.) Chersi, A. (Regina Elena Inst. Cancer Res., Rome, Italy 00161) Natali, P. G. *Fed Proc* 36(3): 1197; 1977. (no refs.)

77-1622 Structural Basis for the Specificity of Phosphorylcholine-binding Immunoglobulins. (Eng.) Padlan, E. A. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014) Davies, D. R.; Rudikoff, S.; Potter, M. *Immunochemistry* 13(11): 945-949; 1976.

A correlation of complementarity region heavy-chain sequences of mouse phosphorylcholine-binding immunoglobulins was made with the known three-dimensional structure of the hapten-binding cavity in one of them (M603). The factor determining the high specificity of the binding of antibody to antigen is the complementarity in the physical-chemical natures of the antigenic determinant and the antibody combining site. Complementarity in the fine physical-chemical attributes of the ligand and binding site was evidenced by the precise positioning of the hapten-contacting protein side groups, which resulted in specific hydrogen-bonding and electrostatic interactions with phosphorylcholine. Complementarity in shape was evidenced by the presence of a deep cavity in the binding site of M603 protein that ensures max surface interaction with hapten. Differences in the hapten-binding properties of proteins can be explained by variations in the primary sequences of the complementarity regions. (31 refs.)

77-1623 Evolution of Immunoglobulin V and C Regions (Meeting Abstract). (Eng.) Barker, W. C. (Natl. Biomedical Res. Foundation, Georgetown Univ. Medical Center, Washington, DC 20007) Ketcham, L. K.; Dayhoff, M. O. *Fed Proc* 36(3): 1239; 1977. (no refs.)

77-1624 The Common Evolutionary Origin of C-Reactive Proteins, Immunoglobulins and Histocompatibility Antigens (Meeting Abstract). (Eng.) Friedenson, B. A. (Univ. Illinois Medical Center, Rush Medical Coll., Chicago, IL 60612) Gewurz, H.; Osmand, A. P. *Fed Proc* 36(3): 1199; 1977. (no refs.)

77-1625 Reaction of Antimembrane Antibodies with the Cell Surface Receptor for IgE (Meeting Abstract). (Eng.) Isersky, C. (Section Chemical Immunology, NIAMDD, NIH, Bethesda, MD 20014) Mendoza, G.; Metzger, H. *Fed Proc* 36(3): 1217; 1977. (no refs.)

77-1626 Autoantibodies to an Altered IgG in Human Breast Cancer. (Eng.) Humphrey, L. J. (Dept. Surgery, Univ. Kansas Medical Center, Rainbow Blvd. at 39th St., Kansas City, KS 66103) Volenec, P. J.; Volenec, F. J.; Cross, D. *J Surg Oncol* 9(1): 29-37; 1977.

Two antibodies in the sera of patients with breast cancer were identified as autoantibodies. Antibody reacting with antigen 1 was present in 10/84 sera, and antibody reacting with antigen 2 was present in 4 sera. Sera from 96 patients with fibrocystic disease and 44 patients with fibroadenoma were tested. Antibody 1 was present in the sera of 2 and antibody 2 in the sera of 15 patients. Sera from 20 breast cancer patients

were tested for cytotoxicity against a reference battery of lymphocytes for determination of activity against transplantation antigens. There was no concordance between the presence or absence of anti-HLA antibodies and the presence or absence of anti-BCA antibodies. One antibody seemed to be directed against IgG(Fab) and the other against IgG(Fc). Anti-IgG(Fab) antibodies occurred in patients with breast cancer as well as other cancers and rarely in patients with noncancerous diseases or in normal screeners of a detection center. The 2-yr survival of breast cancer patients having antibody 1 in their sera was 86% (6/7) compared to 33% (1/3) in those with antibody 2 and 52% (27/52) in patients in whose sera neither antibody 1 nor antibody 2 could be detected by immunodiffusion. The favorable prognosis for the breast cancer patient with serum anti-IgG(Fab) is related to the role of autoantibodies, tumor-bound Ig, and Fc receptor in tumor immunity. (20 refs.)

77-1627 Cytotoxic Antibodies to Leukemia Cells in Normal Human Sera. (Fre.) Dore, J. F. (Centre Leon Berard, 69008 Lyon, France) Bertoglio, J.; Guiout, C. *Ann Immunol (Paris)* 128C(1/2): 155-157; 1977.

Antibodies cytotoxic for the leukemic cells of their children were found in the serum of 10/56 parents of children with acute leukemia (3/24 fathers and 5/25 mothers of children with acute lymphatic leukemia, ALL; 2/3 fathers and 0/4 mothers of children with acute myeloblastic leukemia). Three of the sera had antihistocompatibility antigen activity and were eliminated from the study. Antibodies were also demonstrated in the serum of two normal donors whose serum had induced a partial remission in leukemia and lymphoma patients. The sera from both parents and blood donors were not cytotoxic for the cells of patients in remission or normal lymphocytes. They also did not react with cells from chronic myeloid leukemia or chronic myeloid leukemia patients except when these patients were in blastic crisis. At least one of the sera had cytotoxic activity against the leukemic cells of 55% of the ALL patients tested. The results indicate that normal individuals in the general population as well as parents of leukemic children have been sensitized to antigens associated with leukemia. (8 refs.)

77-1628 Antibodies in Human Sera to Oncornavirus-like Proteins from Normal or Leukemic Marrow Cell Cultures. (Eng.) Louie, S. (Dept. Medicine, Univ. Toronto, Toronto, Canada) Curtis, J. E.; Till, J. E.; McCulloch, E. A. *J Exp Med* 144(5): 1243-1253; 1976.

The immunological characteristics of particles with oncornaviruslike properties, which were identified in human marrow culture supernatants, were examined. Leukemic and nonleukemic marrows were cultured for 5-7 days in the presence of ^{14}C -uridine and either ^3H -leucine or ^3H -glucosamine.

Labeled supernatant components banding in sucrose gradient densities of 1.20-1.24 g/ml were used as antigen in a double-antibody immunoprecipitation assay. Precipitated antigens analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis contained three distinct polypeptides of about 70,000, 45,000 and 30,000 molecular wt. These antigens comigrated with the gp70, gp45, and p30 of a murine leukemia virus. Cross-reactivity with mammalian oncornaviruses was slight. Similar polypeptides were obtained from both leukemic and nonleukemic marrow culture supernates. According to the radioimmunoprecipitation assay, 32/45 leukemic sera, 36/45 normal sera, 15/19 sera from family contacts of leukemic patients, 14/21 cord blood specimens, and 21/23 sera from patients with systemic lupus erythematosus had detectable antibody activity. Eleven leukemic patients were followed for 12 mo, in and out of remission, and none of them showed a change in antibody titer. Four normal laboratory workers also showed no change in antibody titer over 6 mo. The relevance, if any, of this viruslike information and immune response to human leukemia is unclear. (21 refs.)

77-1629 Histamine Release by the Antibodies Against Rat Basophilic Leukemia Cell Membrane (Meeting Abstract). (Eng.) Ishizaka, T. (The Johns Hopkins Univ., Sch. Medicine, Baltimore, MD 21205) Chang, T. H.; Taggart, M.; Ishizaka, K. *Fed Proc* 36(3): 1217; 1977. (no refs.)

77-1630 Purification and Characterization of Isologous Anti-Receptor Antibody for the Response to Phosphorylcholine (Meeting Abstract). (Eng.) Richardson, B. (La Rabida Univ. Chicago Inst., E. 65th St. at Lake Michigan, Chicago, IL 60649) Kohler, H. *Fed Proc* 36(3): 1319; 1977. (no refs.)

77-1631 Production of BALB/c Anti-idiotypic Antibodies Against the BALB/c Myeloma Protein 315 Does Not Require an Intact Ligand-binding Site. (Eng.) Jorgensen, T. (Inst. Medical Biology, Univ. Tromsø Sch. Medicine, Tromsø, Norway) Gaudernack, G.; Hannestad, K. *Scand J Immunol* 6(4): 311-318; 1977.

Seventeen BALB/c mice were immunized with the BALB/c myeloma protein M315, which had been affinity-labeled with bromoacetyldinitrophenyl-L-lysine (BADL) to determine whether the ligand-binding site of M315 is essential for the antiidiotypic response in syngeneic animals. Affinity-labeled M315 (M315 aff) induced antibodies specific for an idiotype determinant in the associated V-L (light) and V-H (heavy chain) domains, but outside the region of M315 that binds dinitrophenyllysine (DNP-L). This idiotype was absent on the isolated L³¹⁵ and H³¹⁵ chains. All the active sides of M315 were blocked by the affinity label. In another experiment, two

groups of mice were immunized with nonaffinity-labeled M315 to determine whether the same idio type was recognized with this immunogen. The 14 animals that were immunized more often and over a longer time interval produced antibodies that could be divided into two populations: 75% directed against the site-associated idio type, 25% against the nonsite idio type. The other group (10 mice) produced site-specific antibodies. It is concluded that the DNP-L binding site is not essential for the development of T helper cells specific for M315 and that M315 carries at least two idiotypes that can be recognized by the B cells of syngeneic animals. (31 refs.)

77-1632 Specific Influence of a Factor in Mouse Plasmacytoma (PC) on Idiotypic (ID) Antibody Response (Meeting Abstract). (Eng.) Bhoopalam, N. (V. A. Hosp. and Univ. Illinois Hosp., Chicago, IL 60612) Heller, P. *Fed Proc* 36(3): 1274; 1977. (no refs.)

77-1633 Isolation of Tumor-Associated Antibodies from Lung Carcinomas and Their Effusions (Meeting Abstract). (Eng.) Paluch, E. (Dept. Pathology, Lenox Hill Hosp., New York, NY 10021) Dorsett, B.; Ioachim, H. L. *Fed Proc* 36(3): 1327; 1977. (no refs.)

77-1634 Stimulation of Phosphate Incorporation into Membrane Phosphatidylinositol in Tumor Cells Treated with Enhancing Antibody (Meeting Abstract). (Eng.) Shearer, W. T. (Dept. Pediatrics, Washington Univ. Sch. Medicine, St. Louis, MO 63110) *Fed Proc* 36(3): 1254; 1977. (no refs.)

77-1635 Antibody to Normal Cells Stimulates Tumor Cells (Meeting Abstract). (Eng.) Heidrick, M. L. (Univ. Nebraska Coll. Medicine, Omaha, NB 68105) Ryan, W. L.; Curtis, G. L. *Fed Proc* 36(3): 1087; 1977. (no refs.)

77-1636 Effect of Inhibiting DNA, RNA and Protein Synthesis of Tumor Cells on Their Susceptibility to Killing by Antibody and Complement (Meeting Abstract). (Eng.) Schlager, S. I. (NIH, Bethesda, MD 20014) Ohanian, S. H.; Borsos, T. *Fed Proc* 36(3): 5220; 1977. (no refs.)

77-1637 Characterization of the Reaction of Anti-Tumor Cell Antibody with Tumor Cells In Vitro (Meeting Abstract). (Eng.) Gill, L. (Northwestern Univ. Medical Sch., Chicago, IL 60611) Anderson, B. *Fed Proc* 36(3): 5220; 1977. (no refs.)

77-1638 Degradation of Tumor Antibodies by Tumor Cells in Culture (Meeting Abstract). (Eng.) Keisari, Y. (Dept. Microbiology, Tel-Aviv Univ., Tel-Aviv, Israel) Witz, I. P. *Fed Proc* 36(3): 1223; 1977. (no refs.)

77-1639 In Vitro Formation of Heterophile Antibodies (Meeting Abstract). (Eng.) Mori, T. (Dept. Micro., SUNY at Buffalo, Sch. Medicine, Buffalo, NY 14214) Milgrom, F. *Fed Proc* 36(3): 1188; 1977. (no refs.)

77-1640 Relationship Between Interferon, Antibody, and Tumor Growth. (Eng.) Baron, S.; Johnson, H. M.; Smith, B. G.; Bukovic, J. A.; Gazdar, A. F. In: *Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias*. NCI and John E. Fogarty International Center for Advanced Study in the Health Sciences pp. 245-249; 1974.

The effect of interferon on the primary immune response was studied. The primary in vitro plaque-forming cell (PFC) response of C57Bl/6J mouse spleen cells to sheep RBC was inhibited by two sources of crude and two sources of highly purified mouse interferon. When interferon was added to cultures at the same time as sheep RBC, max inhibition of the PFC response occurred. Interferon seemed to affect some early event(s) leading to inhibition of the PFC response. The presence of interferon in cultures for the first 4 hr was sufficient to inhibit the PFC response between days 3 and 5. The greater the concentration of interferon added to the cultures the earlier the effect on the PFC response. In studies with *Escherichia coli* 0127 and sheep RBC, polynucleotides inhibited the primary antibody response in proportion to their ability to induce interferon in the spleen cell system. T lymphocyte-produced interferon may function naturally as a mediator for the control of antibody formation and the enhancement of phagocytosis by macrophages. (22 refs.)

77-1641 Enhanced Antibody Affinity in Mice Immunosuppressed by Whole-body Irradiation (Meeting Abstract). (Eng.) Doria, G. (CNEN-Euratom Immunogenetics Group, Lab. Radiopathology, C.S.N. Casaccia (Rome) Italy) Gorini, G.; Di Michele, A.; Adorini, L.; Boraschi, D. *Fed Proc* 36(3): 1231; 1977. (no refs.)

77-1642 **Inhibition of Mouse 3T3 Cell Transformation by Anti-GM₁ Ganglioside and the Presence of "Ganglio-Protein" Complex on 3T3 Cell Surface (Meeting Abstract).** (Eng.) Ng, A. (Biochemical Oncology, Fred Hutchinson Cancer Res. Center and Univ. Washington, Seattle, WA 98104) Tonegawa, Y.; Hakomori, S. *Fed Proc* 36(3): 701; 1977. (no refs.)

77-1643 **High and Low Responses to Basic Protein Among Different Inbred Mouse Strains (Meeting Abstract).** (Eng.) Barnett, L. B. (NIB, NINCDS, NIH, Bethesda, MD 20014) Trotter, J. L. *Fed Proc* 36(3): 1225; 1977. (no refs.)

77-1644 **Detection of Tumor-specific Antigen and Antibody in Kidneys of Neuroblastoma-bearing Mice.** (Eng.) Terman, D. S. (Ben Taub Hosp. Annex 222, Baylor Coll. Medicine, Houston, TX 77030) Durante, D.; Racic, M.; McIntosh, R. M. *Proc Soc Exp Biol Med* 155(1): 137-141; 1977.

The kidneys of neuroblastoma (N)-bearing mice were examined for evidence of glomerular inflammation and immune deposits. Viable C-1300 N cells (10^6) were injected id into 14 A/Jax male mice 10 wk old. Tumors were palpable in the animals on day 7, and they were sacrificed on day 10. All kidney sections showed moderate focal and segmental glomerular mesangial proliferation. Fluorescent microscopy demonstrated diffuse and segmental deposition of mouse immunoglobulin (Ig) and complement in the renal glomerulus. N-specific antigen (Ag) was demonstrated in the glomeruli of tumor-bearing mice with heterologous antisera specific for N; this glomerular staining was abolished completely by absorption of the antisera with N cells. An eluate from the N cells also stained the glomeruli of tumor-bearing mice, and an Ig-containing eluate obtained from the kidneys of tumor-bearing animals stained the tumor. Staining by both eluates was abolished by absorption with viable N cells. These data suggest that the immune deposits in kidneys of N-bearing mice are composed of NAg together with specific antibody, and they support the role of tumor-specific immune reactants as causative factors in the pathogenesis of glomerular inflammatory reactions in N-bearing mice. (14 refs.)

77-1645 **Antibodies to Tumor-Associated Antigens in Sera from Normal Strain-2 Guinea Pigs and Humans (Meeting Abstract).** (Eng.) Brunda, M. J. (Natl. Jewish Hosp. and Res. Center, Denver, CO 80206) Sharpton, T. R.; Minden, P. *Fed Proc* 36(3): 1291; 1977. (no refs.)

77-1646 **The In Vitro Antibody Response to Cell Surface Antigens. Monoclonal Antibodies to Human Leukemia Cells (Meeting Abstract).** (Eng.) Levy, R. (Stanford Medical Sch., Stanford, CA 94305) Dilley, J. *Fed Proc* 36(3): 1254; 1977. (no refs.)

77-1647 **In Vitro Effect of Specific Antigens on Myeloma Tumor Cells (Meeting Abstract).** (Eng.) Kim, B. S. (La Rabida Univ. Chicago Inst., Chicago, IL 60649) Beatty, P. G.; Mallatt, L. *Fed Proc* 36(3): 5220; 1977. (no refs.)

77-1648 **Immunochemical Examination of Soluble Antigens in the Serum of Balb/c Mice Infected with Rauscher Leukaemia Virus.** (Eng.) Toth, F. D. (Inst. Microbiology, Univ. Medical Sch., 4012 Debrecen, Post Office Box 17, Hungary) Vaczi, L.; Kasa, M.; Karsai, T. *Acta Microbiol Acad Sci Hung* 23(2): 185-190; 1976.

The serum of BALB/c mice infected with Rauscher leukemia virus was evaluated. Immune sera prepared in BALB/c mice with or without Freund's adjuvant demonstrated the presence in virus-free leukemic serum of two antigens that differed in their electrophoretic mobility. The antigens were specific for Rauscher leukemia, as they were absent from normal BALB/c serum. Parallel application of anti-Rauscher immune serum and rabbit anti-mouse serum demonstrated that the antigens corresponded in mobility to the α and β globulin fractions. In DBA/1 and 357B1/10 Sn mice, only the α -type antigen was immunogenic, independently of the use of formalinized virus plus Freund's adjuvant, simple formalinized vaccine, or live Rauscher virus. The α and β globulin fractions were isolated by agar block electrophoresis from virus-free leukemic serum. In the double-gel diffusion test, the antigens showed crossing lines and were, therefore, of different specificity. In the α globulin fraction of leukemic serum, the same antigen was detected with immune sera prepared in BALB/c, DBA/1, and C57B1/10 Sn mice. The molecular wt of the α -type antigen was estimated at 40,000, that of the β -type antigen at 120,000. Virus-free leukemic serum and its α and β fractions decreased the activity of the immune serum more than did the control serum. The antigens differ in specificity, and their corresponding determinants are present on the surface of leukemic cells. (20 refs.)

77-1649 **Kinetics and Characterization of Soluble Antigen Induced Tumor Resistance (Meeting Abstract).** (Eng.) Mokyr, M. B. (Northwestern Univ. Medical Sch. and VA Lakeside Hosp., Chicago, IL 60611) Kahan, B. D.; Pellis, N. R. *Fed Proc* 36(3): 1205; 1977. (no refs.)

77-1650 Antigen-Induced Differentiation of Murine Myeloma Cells (Meeting Abstract). (Eng.)

Rohrer, J. W. (Washington Univ. Medical Sch., St. Louis, MO 63110) Lynch, R. G. *Fed Proc* 36(3): 1193; 1977. (no refs.)

77-1651 Adenocarcinoma-associated Antigen: Enhancement of Tumor Growth with Serum from Animals Bearing Adenocarcinoma. (Eng.)

Hakim, A. A. (Abraham Lincoln Sch. Medicine, Dept. Surgery, Post Office Box 6998, Chicago, IL 60680) *J Surg Oncol* 8(5): 383-390; 1976.

The growth of tumors in the presence of tumor-specific cellular immunity was investigated. Five groups of mice received the following pretreatments: (1) phosphate-buffered saline (PBS); (2) adenocarcinoma-specific glycoprotein (gp-AdCa); (3) 10^5 nonviable AdCa cells; (4) serum from normal mice; and (5) serum from AdCa-bearing mice. Twenty-one days later, the mice received 10^5 viable adenocarcinoma cells, which produced solid tumors in all recipients. All animals from Groups 4 and 5 died, but all animals from Group 2 survived. The serum of mice immunized with gp-AdCa inhibited tumor growth, but that of mice with progressive tumors enhanced tumor proliferation. Fourteen days after inoculation of the AdCa cells, animals pretreated with serum from mice bearing progressively growing mammary adenocarcinoma (Group 5) did not develop precipitating antibodies. The spleen cells of these animals did not respond either to gp-AdCa or to phytohemagglutinin, indicating that neither humoral nor cellular immune mechanisms reacted against the invading AdCa cells. This failure in immune response could be attributed to the presence of immunosuppressive factors in the serum of the AdCa-bearing mice used in pretreatment. (13 refs.)

77-1652 Soluble Lymphoma Derived Antigen: Immunogenicity and Reactivity with Anti-Thy-1.2 (Meeting Abstract). (Eng.)

Baechtel, F. S. (Univ. Texas Health Science Center, Dallas, TX 75235) Prager, M. D. *Fed Proc* 36(3): 1261; 1977. (no refs.)

77-1653 Purification and Characterization of Thy 1.1 Alloantigen from Murine T-Lymphoblastoid Cell Lines (Meeting Abstract). (Eng.)

Zwerner, R. K. (Univ. Alabama in Birmingham, Birmingham, AL 35294) Barstad, P. A.; Acton, R. T. *Fed Proc* 36(3): 702; 1977. (no refs.)

77-1654 Distribution of Antigen Used to Induce Active Enhancement of Allografts (Meeting Abstract). (Eng.)

Baldwin, W. M. (Harvard Medical Sch., Boston, MA

02115) Stelos, P.; Tilney, N. L. *Fed Proc* 36(3): 1290; 1977. (no refs.)

77-1655 Antiserum To Lyb-4.1, A Non-H-2 Linked, B Cell Alloantigen Specifically Blocks the MLR Response (Meeting Abstract). (Eng.)

Howe, R. C. (Univ. Massachusetts Medical Sch., Worcester, MA 01605) Freund, J. G.; Rogan, K. M.; Humphreys, R. E. *Fed Proc* 36(3): 1191; 1977. (no refs.)

77-1656 Detection of Histocompatibility Antigens Shown into the Blood by Rat Tumors Growing in Allergic Hosts (Meeting Abstract). (Eng.)

Bale, W. F. (Univ. Rochester Sch. Medicine, Rochester, NY 14642) Contreras, M. A.; Izzo, M. J.; O'Connor, S. *Fed Proc* 36(3): 1293; 1977. (no refs.)

77-1657 Separation of HLA Antigens from Melanoma Associated Antigens Isolated from Culture Melanoma Cells (Meeting Abstract). (Eng.)

McCabe, R. I. (Scripps Clinic and Res. Foundation, La Jolla, CA) Ferrone, S.; Pellegrino, M. A.; Reisfeld, R. A.; Holmes, E. C. *Fed Proc* 36(3): 1293; 1977. (no refs.)

77-1658 Education of Human Lymphocytes Against Mouse Cells: Specific Recognition of H-2 Antigens. (Eng.)

Carnaud, C. (INSERM U 25, Hopital Necker, 161 rue de Sevres, F-75730 Paris Cedex 15, France) Fadiga, G.; Ghotbi, M.; Lesavre, P.; Bach, J. F. *Eur J Immunol* 7(2): 81-85; 1977.

To determine whether xenogeneic reactions involve the recognition of species-defined and/or major histocompatibility complex (MHC)-defined antigens, human peripheral blood lymphocytes (PBL) were xenosensitized against mouse lymphoid cells (1) in vivo, in a local graft-vs-host assay, and (2) in vitro, in a mixed-lymphocyte culture and cell-mediated lympholysis system. Ten million PBL were injected sc in the hind footpads of mice rendered unresponsive by total body irradiation. Seven days later, the popliteal lymph nodes (LN) were dissected, weighed, homogenized, and tested for in vitro cytotoxic activity. In spite of a PBL-induced LN proliferation, no cytotoxicity was detected against the mouse target cells. In contrast, human PBL collected after 7 days of in vitro culture (25×10^6 cells) in the presence of irradiated mouse spleen cells (25×10^6) were strongly cytotoxic against mouse target cells. The mouse antigenic determinants recognized by the PBL were primarily those coded for by the H-2 complex. Only target cells with an H-2 haplotype identical to that of the sensitizing mouse strain or, at least, with a common H-2D end were killed by the xenosensitized PBL.

Mouse target cells from congenic resistant strains remained unaffected. When a population of xenosensitized PBL was depleted of B cells and monocytes, its cytotoxicity was not reduced but, in fact, increased, suggesting the involvement of T cells. (14 refs.)

77-1659 Mapping of a Locus Controlling Cell-Mediated Responsiveness to a Tumor Associated Antigen to the I Region of the H-2 Complex (Meeting Abstract). (Eng.) Meruelo, D. (Dept. Medicine (Immunology), Stanford Univ., Stanford, CA 94305) McDevitt, H. O. *Fed Proc* 36(3): 1202; 1977. (no refs.)

77-1660 A Study of Histocompatibility-2 Antigens in Wild Mice from Santiago, Chile. (Eng.) Pizarro, O. (Unidad de Biología, Facultad de Medicina-Occidente, Universidad de Chile, Casilla 10455, Santiago, Chile) Vergara, U.; Figueroa, F. *Immunogenetics* 4(1): 57-64; 1977.

Wild mice from Santiago, Chile, were assessed by hemagglutination and absorption tests. Some of the wild animals were mated to Brachyury mice, and their offspring were also tested by these tests. A comparison of results obtained with sera anti-H-2.5, 33; anti-H-2.5, 22, 33; anti-H-2.1, 5, 19; and anti-H-2.1, 3, 5, 19 indicated that 19/20 mice were H-2.5-positive. Similarly, H-2.22 could be assigned to 17/22 animals on the basis of positive results with anti-H-2.2, 22, 33 and negative results with anti-H-2.2, 33. The existence of greater polymorphism of H-2, the fact that the H-2.5 antigen was maintained in all the populations, and the absence of H-2 antigens such as H-2.4 were confirmed. Antigens were from either the K or D region of the H-2 complex. Nonexpression of different antigens on RBC was a dominant trait. The antigenic specificities noted were H-2.18, 23, 33, and 22, the last being the most frequent. Antigen H-2.5 was observed more often than antigens H-2.1, 3, and 8. There may be a relationship between the nonexpression of some H-2 antigens and the lack of hemagglutinating HL-A antibodies. (17 refs.)

77-1661 Human B-Lymphocyte Antigens Expressed by Lymphocytic and Myelocytic Leukemia Cells: Lymphocyte-dependent Antibody Studies with Rabbit Antisera. (Eng.) Zebrowski, A. (Dept. Surgery and Medicine, Sch. Medicine, Univ. California, Los Angeles, CA 90024) Billing, R.; Mikulski, S. M.; Gale, R. P.; Terasaki, P. I. *Leukemia Res* 1(1): 13-18; 1977.

The specificity of rabbit antisera raised to papain-solubilized spleen cell-membrane antigens was investigated by the lymphocyte-dependent antibody (LDA) cytotoxicity test. Rabbit antisera had high LDA activity against normal B lymphocytes, but not against T lymphocytes from the same tumor. Antisera were raised in 12 different rabbits to papain digests of malignant spleen cell membranes from 4 patients

with advanced malignant lymphomas. The sera had LDA titers ranging from 10^{-4} to 10^{-8} against B lymphocytes, leukemia cells, and several cultured B-cell lines. The same sera showed no significant reactivity against normal T lymphocytes or the T-cell line Molt 4. The B-cell line superinfected with Epstein-Barr virus was also unreactive. Unlabeled B lymphocytes and acute myeloid leukemia (AML) cells were able to inhibit the LDA activity of the anti-B-cell sera against AML target cells; the same number of T lymphocytes, however, were not inhibitory. LDA effector function could be blocked by pretreatment of the effector lymphocytes with rabbit anti-B serum. Normal rabbit serum and F(ab'), fragments of the anti-B-cell serum did not block effector activity. These results confirm the specificity of the antisera for B cells and certain leukemia cells. (9 refs.)

77-1662 Transplacentally Induced Murine Lung Tumors Express Common Transplantation Antigen Coded for by H-2 Region of the Major Histocompatibility Complex. (Eng.) Martin, W. J. (Bureau Biologics, Bethesda, MD 20014) Gipson, T. G.; Armstrong, R. B.; Butchko, G. M.; Esber, E. C.; Rice, J. M. *Fed Proc* 36(3): 1260; 1977. (no refs.)

77-1663 Immunogenic Properties of Solubilized Tumor Associated Transplantation Antigens (TATA) of Guinea Pig L2C Leukemia (Meeting Abstract). (Eng.) Hu, C. (LI, NIAID NIH, Bethesda, MD 20014) Schwartz, B. D.; Green, I. *Fed Proc* 36(3): 5246; 1977. (no refs.)

77-1664 Possible Tumor Associated Antigens of the Lung (Meeting Abstract). (Eng.) Kempner, D. H. (UCLA, Los Angeles, CA 90024) Stevens, R. H.; Fahey, J. L.; Weimer, H. E. *Fed Proc* 36(3): 1327; 1977. (no refs.)

77-1665 A Widely Crossreacting Tumor Associated Antigen in Carcinoma of Pancreas (Meeting Abstract). (Eng.) Mesa-Tejada, R. (Coll. Physicians/Surgeons, Columbia Univ., New York, NY 10032) Bhattacharyya, J.; Rorat, E.; Fenoglio, C. M.; Klavins, J. V. *Fed Proc* 36(3): 1075; 1977. (no refs.)

77-1666 Tissue Specific and Tumor Specific Antigens in Human Prostate (Meeting Abstract). (Eng.) Wang, M. C. (Roswell Park Memorial Inst., Buffalo, NY 14263) Valenzuela, L.; Murphy, G. P.; Chu, T. M. *Fed Proc* 36(3): 1254; 1977. (no refs.)

77-1667 A Double-Blind Study of the Tissue-Specificity of a Putatively New Antigen Associated with Gastrointestinal Neoplasia (Meeting Abstract). (Eng.) Pant, K. D. (Univ. Kentucky, Lexington, KY. 40506) Goldenberg, D. M.; Herberman, R. B. *Fed Proc* 36(3): 1326; 1977. (no refs.)

77-1668 Detection of T and B Lymphocyte Antigens on Two Major Null Cell Subsets (Meeting Abstract). (Eng.) Kaplan, J. (Dept. Pediatrics, Wayne State Univ. Medical Sch., Detroit, MI 48201) Peterson, W. D. *Fed Proc* 36(3): 1241; 1977. (no refs.)

77-1669 Fluorescent Detection of a Human B-Cell Differentiation Antigen (Ag) On Neoplastic Lymphocytes (Meeting Abstract). (Eng.) Balch, C. M. (Spain Immunology Labs., Dept. Surgery, Univ. Alabama in Birmingham, Birmingham, AL) Dougherty, P. A.; Vogler, L.; Cresswell, P. *Fed Proc* 36(3): 1317; 1977. (no refs.)

77-1670 Isoantigens A, B, H in Transitional Cell Tumors of the Urinary Bladder (Meeting Abstract). (Eng.) Limas, C. (VA Hosp. and Univ. Minnesota, Minneapolis, MN 55417) Lange, P. H.; Vessella, R.; Fraley, E. E.; Azar, M. M. *Fed Proc* 36(3): 1327; 1977. (no refs.)

77-1671 Regulation of Xenotropic Murine Leukemia Virus (MuLV-X) Antigen Expression in DBA/2 Mice (Meeting Abstract). (Eng.) Morse, H. C. (NIAID and NIDR, NIH, Bethesda, MD) Chused, T.; Hartley, J. W.; Taylor, B. *Fed Proc* 36(3): 1249; 1977. (no refs.)

77-1672 In Vitro Biosynthesis of Cellular ABO Antigens. Defective Expression on Neoplastic Cells (Meeting Abstract). (Eng.) Kuhns, W. J. (New York Univ. Sch. Medicine, New York, NY 10016) *Fed Proc* 36(3): 5220; 1977. (no refs.)

77-1673 Three Classes of CEA Antigenic Determinants Expressed by Membrane-Associated CEA (Meeting Abstract). (Eng.) Leung, J. P. (Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Plow, E. F.; Edgington, T. S.; Nakamura, R. M. *Fed Proc* 36(3): 1326; 1977. (no refs.)

77-1674 Plasma CEA, Tumor CEA, and Tumor Histology. (Eng.) Boyd, C. R. (Albert Chandler Medical Center, Dept. Surgery, Univ. Kentucky, Lexington, KY 40506) Bivens, B. A.; Kashmiri, R.; Parker, J. C.; Meeke, W. R. *J Surg Oncol* 8(6): 507-512; 1976.

The carcinoembryonic antigen (CEA) concentration in preoperative plasma, tumor tissue, and normal bowel distant from the tumor and tumor histopathology were examined in 35 patients in an effort to define the relationship of CEA and colorectal carcinoma. There was no correlation between plasma CEA and tumor CEA. The tumors were arbitrarily divided into two groups using a level of 1.0 μg CEA/mg tissue protein to separate tumors with a low CEA concentration from those with a high level. A total of 34% of the tumors as well as two autopsy specimens of normal bowel had levels of < 1.0 μg CEA, but the remaining 66% had much higher concentrations of CEA, with a range of 1.11-11.5 μg . No differences were noted between the low- and high-concentration groups with respect to histopathological characteristics. No difference was demonstrated when histopathological findings were compared to abnormal and normal plasma CEA values. It is concluded that CEA is not tumor-specific, elevated CEA levels are not a constant finding in colorectal carcinoma, tumor CEA levels do not seem to correlate with histologic degree of tumor differentiation, increased plasma CEA levels do not necessarily connote increased tumor CEA level and, conversely, normal plasma CEA levels do not necessarily mean low tumor CEA levels. (15 refs.)

77-1675 Fetal Antigens Associated with Adenovirus 12 Mouse Tumors. (Eng.) Akagi, T. (Kochi Prefectural Cancer Inst., Kochi Prefectural Central Hosp., 2-7-32 Sakuraicho, Kochi 780, Japan) *Acta Med Okayama* 30(6): 385-395; 1976.

An investigation was made to determine the relationship of fetal antigens, which are common to a variety of tumors, to tumor-specific transplantation antigens. Conflicting results have been reported as to whether fetal antigens can elicit transplantation immunity in syngeneic hosts. The fetal antigen(s) of C3H/BiF/Ki mouse tumor cells induced by adenovirus 12 (Ad12) was examined by transplantation resistance, local adoptive transfer, and in vitro cell-mediated microcytotoxicity tests. When syngeneic mice immunized with irradiated, days 8-9 fetal cells were challenged sc with 10^4 tumor cells, a slight inhibition of tumor incidence (23.1%) occurred. Upon challenge with 5×10^4 cells, however, immunization with days 8-9 or 13-14 fetal cells had no effect. Tumor growth, on the other hand, was inhibited significantly in mice immunized with days 8-9 fetal cells. Local adoptive transfer of multiparous (mp) and primiparous (pp) pregnant mouse spleen cells mixed with tumor cells (ratio of 200 and 400:1) had no effect on tumor incidence, but both samples of mp cells but only 1/3 pp samples inhibited tumor growth slightly. In the microcytotoxicity test, spleen cells

from mice immunized with day 11-12 fetal cells and from mp or pp pregnant mice showed a cytotoxic effect on AD12-derived MT-2 cells and mouse fetal cells, but not on newborn mouse kidney cells. These results suggest the presence of phase-specific tumor-associated fetal antigen(s) that can evoke transplantation immunity. (33 refs.)

- 77-1676 Membrane Associated Antigens of Human Malignant Melanoma III. Specificity of Human Sera Reacting with Cultured Melanoma Cells.** (Eng.) Seibert, E. (Abteilung für Experimentelle Dermatologie, Universitäts-Hautklinik, 4400 Münster, W. Germany) Sorg, C.; Happle, R.; Macher, E. *Int J Cancer* 19(2): 172-178; 1977.

Sera from melanoma patients, pregnant women, healthy donors, and patients with tumors other than melanoma were tested on various melanoma lines and on cultured brain tumor and adult skin fibroblast, using a microimmune adherence test. Sera from normal donors, tumor patients, and melanoma patients that reacted against at least one melanoma line were selected and tested against various melanoma cell lines as well as against a brain tumor and skin fibroblasts. The percentage of positively reacting sera varied from cell line to cell line. The positively reacting sera were absorbed in addition to the AB Rh+ absorption with pooled platelets of approx 200 donors. When the sera were absorbed with pooled cells from 6- to 8-wk-old fetuses, there was a high frequency of antibodies in females and males against fetal antigens also expressed on melanoma cells. Absorptions with three different melanoma cell lines, a brain tumor, and fibroblasts were carried out. There was only partial cross-reactivity among the different cell lines. There is no evidence for the presence of cross-reacting tumor-reactivity among the different cell lines. There is no evidence for the presence of cross-reacting tumor-specific antigens. (21 refs.)

- 77-1677 Human Membrane Associated Antigens Extractable from Lung Tumors with Triton X-100 (Meeting Abstract).** (Eng.) Veltri, R. W. (Div. Otolaryngology, West Virginia Univ., Morgantown, WV 26506) Maxim, P. E. *Fed Proc* 36(3): 1327; 1977. (no refs.)

- 77-1678 Purification of a Human Lung Tumor Associated Antigen (Meeting Abstract).** (Eng.) Braatz, J. A. (NIH, Bethesda, MD 20014) McIntire, K. R.; Princler, G. L.; Kortright, K. H.; Herberman, R. B. *Fed Proc* 36(3): 867; 1977. (no refs.)

- 77-1679 Partial Purification of a Breast Cancer Associated Antigen, by Dissociation of Immune**

Complexes (Meeting Abstract). (Eng.) Sulitzeanu, D. (Medical School, Jerusalem, Israel) Gorsky, Y.; Mugraby, L.; Morecki, S. *Fed Proc* 36(3): 1326; 1977. (no refs.)

- 77-1680 Purification and Characterization of a Glycoprotein from Human Breast Cancer Cells (Meeting Abstract).** (Eng.) Martens, C. L. (Univ. Iowa, Iowa City, IA 52242) Butler, J. E. *Fed Proc* 36(3): 491; 1977. (no refs.)

- 77-1681 A New Glycoprotein Possibly Involved in Antigen Masking at the Surface of a Murine Carcinoma Ascites Cell (Meeting Abstract).** (Eng.) Codington, J. F. (Harvard Medical Sch., Boston, MA 02114) Cooper, A. G.; Miller, D. K.; Brown, M. C.; Jeanloz, R. W. *Fed Proc* 36(3): 824; 1977. (no refs.)

- 77-1682 Detection of Antigens to Rous Virus-transformed Cells by Direct Lymphocyte Immunotoxicity.** (Fre.) Dambrine, G. (Institut national de la Recherche agronomique, Station de Pathologie aviaire, Centre de Recherches de Tours, 37380 Monnaie, France) Cauchy, L. *C R Acad Sci [D] (Paris)* 284(15): 1477-1479; 1977.

Labeling of target cells with ^3H -proline was used to measure the cytotoxicity of lymphocytes from Syrian hamsters immunized with Prague strain Rous sarcoma virus (RSV)-induced rat tumor cells (XC) against BHK 21-13 hamster cells transformed by Schmidt-Ruppin RSV (RS 2-3 and RS 2-10 cells). Nontransformed BHK 21-13 hamster cells served as control target cells, and lymphocytes from uninoculated Syrian hamsters were compared for cytotoxic effects. Immune lymphocytes were obtained from hamsters inoculated with two ip injections of killed XC cells followed by three sc injections of live XC cells at 15-day intervals. The target cells were incubated with ^3H -proline, specific activity 20-30 Ci/mM, so that the final concentration was 100 μCi /1 million cells. The culture medium was Eagle's minimum essential medium deprived of L-proline, in order to ensure max uptake of ^3H -proline. After exposure of the target cells to immune or nonimmune lymphocytes for 48 hr, the radioactivity of the remaining cells was measured with a Beckman counter. The cytotoxicity of the immune lymphocytes for the RS 2-3 and RS 2-10 cells was greater than that for the untransformed BHK 21-13 cells, indicating the presence of surface antigens recognized by the lymphocytes. The percentage of cell death was directly related to lymphocyte concentration. (12 refs.)

- 77-1683 Effect of MULV on IA Antigen Expression (Meeting Abstract).** (Eng.) Sharpe, M. R. (Univ. South Alabama, Mobile, AL 36617) David, C. S.; Peterson, R. D. *Fed Proc* 36(3): 1085; 1977. (no refs.)

- 77-1684 **Immunogenetics of the Qa-2 Locus of the Mouse (Meeting Abstract).** (Eng.) Flaherty, L. (NY State Dept. Health, Div. Labs. and Res., Albany, NY 12201) *Fed Proc* 36(3): 1195; 1977. (no refs.)
- 77-1685 **MLC Response to Tla-Region Determinants (Meeting Abstract).** (Eng.) Sullivan, K. (NY State Dept. Health, Div. Labs. and Res., Albany, NY 12201) *Fed Proc* 36(3): 1191; 1977. (no refs.)
- 77-1686 **Genetic Control of Responses to Moloney Leukemia Virus (M-MuLV) in Rats (Meeting Abstract).** (Eng.) Jones, J. M. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA 92037) Jensen, F.; Feldman, J. D. *Fed Proc* 36(3): 1223; 1977. (no refs.)
- 77-1687 **Inhibition of Lectin Induced Mitogenesis of Lymphocytes by Cultured Lymphocyte Surface Glycoproteins (HGP) and Antibodies to HGP (Meeting Abstract).** (Eng.) Hurwitz, M. Y. (Dept. Biochemistry, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455) Paulson, C. D.; O'Brien, K. J.; Prody, C. A.; Edstrom, R. D. *Fed Proc* 36(3): 795; 1977. (no refs.)
- 77-1688 **Chemical and Immunological Studies of Cell Surfaces from Normal and Transformed Cells (Meeting Abstract).** (Eng.) Kamm, A. R. (Univ. Arizona, Tucson, AZ 85724) Van Nest, G.; Grimes, W. J. *Fed Proc* 36(3): 824; 1977. (no refs.)
- 77-1689 **Membrane Characteristics of Mitogen-Stimulated Lymphoblastoid Lines (Meeting Abstract).** (Eng.) Dwyer, J. M. (Yale Univ. Sch. Medicine, New Haven, CT 06510) Evans, A. S. *Fed Proc* 36(3): 1232; 1977. (no refs.)
- 77-1690 **Effects of "Immune" RNA on Lymphocytes Obtained from Tumor-Bearing Mice (Meeting Abstract).** (Eng.) Pennline, K. J. (Dept. Microbiology, The Ohio State Univ., Columbus, OH 43210) Dodd, M. C. *Fed Proc* 36(3): 1242; 1977. (no refs.)
- 77-1691 **Isolation, Purification and Cell-free Translation of Immunoglobulin Messenger RNAs from Immunoglobulin Producing Cells and Variants.** (Eng.) Pestka, S.; Bailey, L.; Brandsch, R.; Graves, P.; Green, M.; Jilka, R.; McInnes, J.; Okuyama, A.; Tucker, P.; Weiss, D.; Yaffe, L.; Zehavi-Willner, T. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 121-143; 1976.
- Immunoglobulin (Ig) biosynthesis and gene expression were assessed by concentrating on the isolation, purification, and cell-free translation of messenger RNA's (mRNA) for both the heavy and light chains of myeloma proteins. Cell-free translation of Ig mRNA from MOPC-315 plasmacytoma and MOPC-315 variants was examined. No light (L³¹⁵) or immunoprecipitable L³¹⁵ fragments were noted in the cell-free products directed by any of the MOPC-315 NP-1 mRNA fractions. This observation excluded the existence of a specific defect in the translational or posttranslational apparatus of the variant, as well as the existence of a specific protein inhibitor of L³¹⁵ mRNA translation. No translatable poly-A-containing mRNA capable of directing the synthesis could be extracted from the MOPC-315 NP-1 plasmacytoma. The data obtained should help elucidate the coordination between genetic information and the cellular machinery for macromolecular biosynthesis and processing that is necessary for the production of functional Ig molecules. (43 refs.)
- 77-1692 **The Relationship of Myeloma "RNA" to the Immune Response.** (Eng.) Heller, P.; Bhoopalam, N.; Chen, Y.; Yakulis, V. In: *Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 223-233; 1976.
- A correlation between the immune response and myeloma RNA was evaluated. The peripheral blood lymphocytes of BALB/c mice with MOPC 104E myeloma were tested for the immunochemical characteristics of surface immunoglobulin (Ig) at weekly intervals after tumor implantation. The percentages of lymphocytes with normal surface Ig gradually decreased and those with idiotypic surface Ig increased. Surface Ig of the 104E IgM idiotype was found on 4% of the lymphocytes before and on 32% after incubation with MOPC 104E RNA. In vivo experiments, 72 hr after the injection of 200 µg of MOPC 104E RNA, the proportion of peripheral lymphocytes with 104E IgM surface Ig was max and decreased thereafter. The response to 1 µg of dextran in animals inoculated with RNA degraded by ribonuclease was comparable to the response obtained in control mice without prior RNA injection. Although MOPC 104E RNA increased the immune response to 1 µg of dextran to the same level as 8 µg in control mice, amounts of dextran > 1 µg did not further increase it. When MOPC 104E RNA was given 72 hr prior to the injection of other antigens, a significant immunosuppressive effect was noted. The findings do not exclude the possibility that the injection of plasmacytoma RNA affects the suppressor or helper function of T cells. (34 refs.)
- 77-1693 **An In Vitro Model for Transfer of Tumor Specific Sensitivity with "Tumor Immune" RNA**

Extracts and Localization of Immunologically Active RNA Fractions. (Eng.) Paque, R. E. *In: Immune RNA in Neoplasia*. Fink, M. A., ed. (New York: Academic Press, Inc.): pp. 235-244; 1976.

Studies on the development of an in vitro model for the transfer of tumor-specific sensitivity with RNA extracts are summarized, along with experiments designed to isolate and localize the immunobiologically active fraction contained in the RNA extracts. The data indicate that tumor-specific sensitivity for guinea pig line-10 or line-1 hepatoma tumor cell antigens can be transferred with RNA extracts to nonsensitized peritoneal exudate cells, as assessed by the cell-migration-inhibition correlate of delayed hypersensitivity. The immunologically active fraction from the RNA extracts responsible for transferring tumor-specific sensitivity to peritoneal exudate cells was localized and isolated. A fraction isolated between the 4S and 18S peaks of a sucrose density gradient was able to transfer line-10 or line-1 sensitivity to the cells. The results depended on the presence of high-molecular-wt RNA in the RNA extracts. (16 refs.)

77-1694 Further Characterization of a Bacterial Tumor Isolate: Production of a Human Chorionic Gonadotropin-Like Substance (Meeting Abstract). (Eng.) Affronti, L. F. (George Washington Univ. Medical Center, Washington, DC 20037) Grow, L.; Brumbaugh, R.; Chu, Y. M. *Fed Proc* 36(3): 1256; 1977. (no refs.)

77-1695 Human Chorionic Gonadotropin: Doubtful Role as an Inhibitor of Cell-mediated Immunity. (Eng.) Bean, M. A. (Virginia Mason Res. Center, 1000 Seneca, Seattle, WA 98101) Salser, J. S.; Newman, M.; Stahl, K.; Balis, M. E. *Cancer Immunol Immunother* 2(2): 85-90; 1977.

Human chorionic gonadotropin (HCG) preparations were tested for their ability to inhibit mitogen-induced lymphocyte blastogenesis. Wide variations were found in ability to suppress phytohemagglutinin response, in toxicity to lymphocytes, and in antitryptic activity. High concentrations of a preparation low in toxicity and trypsin inhibitor did not suppress blastogenesis, indicating that HCG may not be a potent inhibitor of cell-mediated immunity. The inhibitory effect of HCG commonly observed may be due to contaminants of the HCG preparations used in the assay systems. (20 refs.)

77-1696 Inhibition of Antibody-Complement Killing of Tumor Cells by Concanavalin A (Meeting Abstract). (Eng.) Boyle, M. D. P. (NIH, Bethesda, MD 20014) Langone, J. J. *Fed Proc* 36(3): 1283; 1977. (no refs.)

77-1697 The Effect of Cell-Free Ehrlich Ascites Tumor Fluid on the Lymphocyte Response to Phytohemagglutinin and Concanavalin A (Meeting Abstract). (Eng.) LeBien, T. W. (Univ. Nebraska, Medical Center, Omaha, NB 68105) McCarthy, R. E. *Fed Proc* 36(3): 1218; 1977. (no refs.)

77-1698 Agglutination by Glycogen-Concanavalin A Complex (Meeting Abstract). (Eng.) Wang, P. Y. (Univ. Toronto, Toronto, Ontario M5S 1A8, Canada) Evans, D. W. *Fed Proc* 36(3): 795; 1977. (no refs.)

77-1699 Altered DNA Synthesis and Viability of Human Leukemic Lymphoid Cells Cultured with Concanavalin A (ConA) (Meeting Abstract). (Eng.) Richie, E. (M.D. Anderson Hosp., Houston, TX 77030) *Fed Proc* 36(3): 1254; 1977. (no refs.)

77-1700 Ultrastructural and Quantitative Evaluation of Concanavalin A Receptors on the Surface of Mouse Leukaemia Cells Cultivated in Vivo and in Vitro (Meeting Abstract). (Eng.) Bartoszewicz, W. (Dept. Tumour Biology Inst. Oncology, Warszawa, Poland) Rossowski, W.; Matyja, H.; Radzikowski, C. *Folia Histochem Cytochem (Krakow)* 14(4): 359-360; 1976. (1 ref.)

See also:

- * (Rev.): 77-1228, 77-1236, 77-1237, 77-1238, 77-1239, 77-1240, 77-1241, 77-1242, 77-1243, 77-1244, 77-1245, 77-1246, 77-1247.
- * (Chem.): 77-1283.
- * (Phys.): 77-1430, 77-1431, 77-1432, 77-1436, 77-1460.
- * (Viral): 77-1487, 77-1494, 77-1498, 77-1499, 77-1506, 77-1508, 77-1510, 77-1511, 77-1515, 77-1519, 77-1523, 77-1534, 77-1537, 77-1539, 77-1540, 77-1543, 77-1544, 77-1547, 77-1548, 77-1551, 77-1554, 77-1556, 77-1559.
- * (Path.): 77-1703, 77-1705, 77-1707, 77-1717, 77-1727, 77-1737.

PATHOGENESIS

77-1701 Chromosome 14 Translocation in African and North American Burkitt's Lymphoma. (Eng.)

Kaiser-McCaw, B. (Div. Medical Genetics, Dept. Pediatrics, Crippled Children's Div., Child Development and Rehabilitation Center, Univ. Oregon Health Sciences Center, Portland, OR 97201) Epstein, A. L.; Kaplan, H. S.; Hecht, F. *Int J Cancer* 19(4): 482-486; 1977.

Chromosome-banding techniques were used to study chromosome translocations in three African and two North American Burkitt's lymphoma cell lines. In the North American line SU-AmB-1, the majority of the cells (65%) contained 46 chromosomes and they were pseudodiploid. All cells showed a translocation between chromosomes 8 and 14. Complex translocations involving chromosomes 4, 5, and 7 were also observed. A minority (35%) of the cells had 47 chromosomes and an additional copy of one of the translocation chromosomes derived from number 4. SU-AmB-2 cells were all pseudodiploid, with a translocation between chromosomes 8 and 14. The African Burkitt's lymphoma cell line EB3 was karyotypically indistinguishable from SU-AmB-2. All HR-1 cells had 47 chromosomes, including the 8;14 translocation. These cells were karyotypically the same as SU-AmB-2, except for an additional marker chromosome that was submetacentric and the size of number 7. Raji had the same karyotype as SU-AmB-2, including the 8;14 translocation plus two other markers, one the size of number 3 and the other the size of number 18. The 8;14 translocation may be an important event in the development of human lymphocytic malignancy analogous to the occurrence of the Philadelphia chromosome in chronic myelogenous leukemia. (26 refs.)

77-1702 Origin of the Translocated Segment of the 14q+ Marker in Non-Burkitt Lymphomas. (Eng.)

Mark, J. (Dept. Pathology, Central Hosp., Skovde, Sweden) Ekedahl, C.; Hagman, A. *Hum Genet* 36(3): 277-282; 1977.

Cytogenetic studies were made in two cases of histiocytic lymphoma. G-banding revealed a stemline with a 14q+ marker in both tumors. The origin of the extra segment on No. 14 was different in the two cases. These observations and those reported in the literature indicated an inconsistent pattern for the origin of the extra material on No. 14. The common feature in all cases was instability of the distal region of the long arm of No. 14, with liability of this region to be involved in structural rearrangements, particularly translocations. (10 refs.)

77-1703 Histiocytic Lymphoma of B Cell Origin. (Eng.)

Goldberg, J. (Dept. Medicine, Div. Hematology

and Oncology, State Univ. New York, Upstate Medical Center, Syracuse, NY 13210) Davey, F. R.; Gottlieb, A. J. *Arch Intern Med* 137(6): 800-803; 1977.

A diffuse histiocytic lymphoma with a terminal leukemic phase occurred in a 50-yr-old man who was first admitted with asymptomatic right cervical lymphadenopathy. One year later, the patient was readmitted with a rapidly enlarging right axillary mass; right axillary dissection produced a nodular mass and three small satellite lymph nodes. Upon microscopic examination, a diffuse infiltrate of large pleomorphic cells with a moderate amount of cytoplasm was found. The nuclei were enlarged and the nuclear membranes were thickened. Nucleoli were prominent. The neoplastic cells diffusely infiltrated the parenchyma of the lymph node, capsule, and surrounding tissue. These findings were interpreted as diffuse histiocytic lymphoma. Cytochemical studies showed that the neoplastic cells had the profile of lymphocytes. Only 6% of the axillary mass cell suspension yielded spontaneous rosette-forming lymphocytes. Rosette-forming cells were also markedly reduced in the peripheral blood sample. Most of the neoplastic cells from the axillary mass, a bone marrow aspirate, and the peripheral blood carried surface immunoglobulin (Ig); ie, B-cell markers. Immunologic studies made 1 yr later in the leukemic phase of this disorder showed that most of the neoplastic cells carried IgM λ . (31 refs.)

77-1704 Characterization of EBV-Genome Negative "Null" and "T" Cell Lines with respect to tumor

incidence, time to palpable tumor (latency period), from Children with Acute Lymphoblastic Leukemia and Leukemic Transformed Non-Hodgkin Lymphoma. (Eng.) Schneider, U. (Kinderklinik der Universität Erlangen-Nürnberg, D-8520 Erlangen, Loschgestr., W. Germany) Schwenk, H. U.; Bornkamm, G. *Int J Cancer* 19(5): 621-626; 1977.

From 62 explants from peripheral blood, bone marrow and cerebral fluid of children with acute lymphoblastic leukemia (ALL) and leukemic transformed non-Hodgkin lymphoma (NHL) cultivated for at least 8 wk, eight permanently growing cell lines were obtained. Of these, five were EBNA (Epstein-Barr virus-specific nuclear antigen)-positive; three were EBNA-negative and lacked Epstein-Barr virus genomes. Two cell lines expressed neither B nor T cell characteristics. One line expressed T cell characteristics and complement receptors. The pattern of cytochemical staining of the growing lymphatic cells was identical to that of membrane receptors of lymphoblasts from the same donor prior to cultivation. All leukemic cell lines were derived from patients in relapse, while cells from patients revealing the first manifestation of the disease did not proliferate; this seems to demonstrate the enhanced growth potential of lymphoblasts that have resisted prior antileukemic therapy. (30 refs.)

77-1705 Immunologic and Histopathologic Study of Non-hodgkin's Lymphomas (Meeting Abstract).

(Eng.) Brubaker, D. B. (Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA 15261) Whiteside, T. L.; Rabin, B. S. *Fed Proc* 36(3): 1054; 1977. (no refs.)

77-1706 Metastatic Patterns of Cancers of the Lymphopoietic System in Man. (Eng.) Viadana, E.

(Dept. Biostatistics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263) *J Surg Oncol* 8(6): 489-499; 1976.

The distribution of metastases at specific sites in three types of malignant lymphoma was examined. The autopsy records of 358 patients with reticulum cell sarcoma, lymphocytic lymphosarcoma, or Hodgkin's disease were analyzed. The reticulum cell sarcoma demonstrated an excess of metastases in the breast and skin compared to Hodgkin's disease and lymphocytic lymphosarcoma. When metastases were located in the head, neck, and chest, the metastatic pattern of the three malignant lymphomas seemed to be similar, irrespective of the type of organ involved. The lymphocytic lymphosarcoma demonstrated an excess of metastases in the pericardium, whereas Hodgkin's disease showed a deficiency of malignant cells in the heart muscle. The metastatic patterns of lymphocytic lymphosarcoma and reticulum cell sarcoma seemed to be markedly different from those of Hodgkin's disease. The lymphocytic and reticulum cell lymphosarcoma were more widespread than Hodgkin's disease, but the patterns of pelvic and abdominal metastases strongly suggested either their multifocal origin or a different sequence of events in the seeding of lymph node areas, compared to those of Hodgkin's disease. There is a relationship between blood-borne metastases and the degree of anaplasia of certain lymphomas. (14 refs.)

77-1707 "Sternberg-Reed" Giant Cells of Hodgkin's Disease: Cultivation In Vitro, Heterotransplantation, and Characterization as Neoplastic Macrophages.

(Eng.) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305) Gartner, S. *Int J Cancer* 19(4): 511-525; 1977.

Spleen cells from 25 patients with Hodgkin's disease were grown in long-term culture and compared with control cultures of normal spleen macrophages. The Hodgkin's spleen cell cultures contained mono-, bi-, and multinucleate giant cells, many of which resembled Sternberg-Reed cells. The cells were neoplastic by the dual criteria of aneuploidy and heterotransplantability in the brains of nude mice. They adhered to cultured vessel surfaces, phagocytized India ink and antibody-coated sheep RBC, and secreted lysozyme. The giant cells possessed both Fc and complement (C-3b) receptors, but they lacked lymphocyte markers such as C-3d receptors, surface immunoglobulin M, and the capacity to form erythrocyte rosettes. The mono-, bi-, and multinucleate

cells readily synthesized DNA, and binuclear mitotic figures were observed. It is concluded that these cells are the in vitro descendants of the Sternberg-Reed and Hodgkin's cell population and that they derive from macrophages or closely related cells of the mononuclear phagocyte system. (74 refs.)

77-1708 Hypokalemia in Leukemia (Letter to Editor).

(Eng.) Fisher, J. R. (Dept. Medicine, Phoenix Indian Medical Center, Phoenix, AZ 85016) *Ann Intern Med* 86(3): 363-364; 1977.

The case histories of a 16-yr-old boy and a 17-yr-old girl, each with acute lymphoblastic leukemia and associated hypokalemia, are presented. It is suggested that there may be direct renal invasion by leukemic cells in some patients; the associated renal K loss may cause the hypokalemia. (4 refs.)

77-1709 Abnormal Granulocyte Feedback Regulation of Colony Forming and Colony Stimulating Activity-producing Cells from Patients with Chronic Myelogenous Leukemia. (Eng.) Broxmeyer, H. E. (Sloan-Kettering Inst. Cancer Res., Section 6136, 410 E. 68th St., New York, NY 10021) Mendelsohn, N.; Moore, M. A. *Leukemia Res* 1(1): 3-12; 1977.

The negative feedback regulation of granulocyte proliferation was investigated using polymorphonuclear neutrophils (PMN) from 58 patients with chronic myelogenous leukemia (CML). CML PMN were quantitatively deficient in colony-inhibiting activity (CIA), which reduces the number of bone marrow and blood cells that can spontaneously proliferate in vitro to form colonies and clusters. This deficiency existed regardless of the patient's clinical status or in vitro growth patterns. Further extraction of CIA by high-speed centrifugation demonstrated a suppressor material of CIA in the pellet from normal PMN extracts that could only be found in 1/27 extracts from CML PMN. Removal of the pellet also decreased the 37 C temperature sensitivity of normal CIA. The CIA of CML PMN and normal PMN had the same site of action. CML CIA was specific in its nontoxic action on the colony-stimulating activity (CSA)-producing cells. Neither colony-forming cells nor cell-free CSA molecules were affected. Target cells (density < 1.070 g/cm³) from CML patients were less sensitive than normal targets to inhibition with low concentrations of CIA from normal PMN. High concentrations of CIA, however, were equally active against CML and normal targets. If the feedback regulation of granulocyte proliferation has in vivo significance, it may be possible to control the progress of this disease physiologically. (19 refs.)

77-1710 Chromosome Banding Patterns of 49 Cases of Chronic Myelocytic Leukemia (Letter to Editor).

tor). (Eng.) Engel, E. (Vanderbilt Univ., Sch. Medicine, Nashville, TN 37232) McGee, B. J.; Myers, B. J.; Flexner, J. M.; Krantz, S. B. *N Engl J Med* 296(22): 1295; 1977.

Cytogenetic studies were performed on bone marrow samples from 49 patients (17 women and 32 men, av age 52 yr) with chronic myelocytic leukemia (CML). The following cytogenetic patterns were found: the Philadelphia chromosome (Ph¹) with a 9;22 translocation in 38 patients; no anomalies in 4; other anomalies without Ph¹ in 3; Ph¹ with a translocation on a segment other than 9q in 2; and a masked Ph¹ with various translocations in 2. The implications of these cytogenetic features remain unknown. (10 refs.)

77-1711 Specific Routes of Chromosome Evolution in Chronic Myeloid Leukemia and Other Human Neoplastic Disorders (Meeting Abstract). (Eng.) Levan, G. (Inst. Genetics, Univ. Lund, Lund, Sweden) Mitelman, F. *Hereditas* 84(2): 244-245; 1977. (no refs.)

77-1712 Morphological Observation of Murine Leukemia Cells with Scanning Electron Microscope (Meeting Abstract). (Eng.) Ichikawa, H. (Dept. Virology, Okayama Univ. Medical Sch., Okayama, Japan) Fugio, K.; Uno, F.; Akatuka, K.; Tawara, J. *J Electron Microsc (Tokyo)* 25(3): 185; 1976. (no refs.)

77-1713 IgD Myeloma and Acute Myelomonocytic Leukemia (Letter to Editor). (Eng.) Goldfarb, S. B. (Detroit General Hosp., Wayne State Univ. Sch. Medicine, Detroit, MI 48226) Bishop, C. R. *Blood* 49(3): 489-490; 1977.

The association of acute myelomonocytic leukemia with the IgD form of myeloma is reported for the first time. The patient, a 57-yr-old woman, died 5 yr after her initial presentation. (4 refs.)

77-1714 Familial Leukemia. (Fre.) Khitri, A. (Service d'Hematologie, Centre Hospitalier Universitaire, Hopital Benbadis, Constantine, Algeria) Benlatrache, K.; Aouati, A.; Messerschmitt, J. *Sem Hop Paris* 53(16): 916-918; 1977.

A family is described in which two deaths, in a young woman aged 22 yr and, 2 yr later, in her brother, aged 16, were the result of acute myeloblastic leukemia. A third brother had probably died of the disease 10 yr earlier at age 21. The parents, who were first cousins, were in good health at the ages of 61 and 53, and there were 3 living children aged 21, 15,

and 13 yr of a total of 12. Five of the children had died before the age of 1 yr. Leukemic families are rare, and only 137 have been reported in the literature published between 1861 and 1968. Particularly unusual is the occurrence of leukemia in more than two family members. (18 refs.)

77-1715 Small F Chromosome in Myelo- and Lymphoproliferative Diseases. (Eng.) Whang-Peng, J. (Building 10, Room B6-10, NCI, NIH, Bethesda, MD 20014) Gralnick, H. R.; Knutsen, T.; Brereton, H.; Chang, P.; Schechter, G. P.; Lessin, L. *Leukemia Res* 1(1): 19-30; 1977.

A small F chromosome was observed in five patients with various myelo- and lymphoproliferative diseases, and studies were undertaken to determine whether there is a correlation among this chromosome abnormality and diagnosis, response to therapy, and/or prognosis. Case histories are presented for the five patients, three of whom had a small F chromosome with both arms deleted, 19p-q-. Each of these patients had a different disease: acute myelomonocytic leukemia, lymphosarcoma, and erythroleukemia. One patient had a hyperplastic marrow and erythroid hyperplasia for a year prior to the development of acute myelogenous leukemia and a small F chromosome with del(20)(q12). The fifth patient had sideroblastic anemia, which terminated in erythroleukemia; no banding studies were available. These findings suggest that there is a high incidence of F-chromosome abnormalities in patients with abnormal erythropoiesis. The existence of the small F chromosome in three nonmalignant marrows suggests that it acts like the Philadelphia chromosome in chronic myelogenous leukemia; ie, it does not disappear when the disease is in remission. The cells with a small F are rather stable, and they can gradually replace cytogenetically normal cells without affecting the clinical course of the disease. It is the emergence of additional chromosomal abnormalities in these cells that signals a poor prognosis. (19 refs.)

77-1716 Polycythemia Vera Associated with Raised Concentrations of Haemoglobin F (Letter to Editor). (Eng.) Hoffman, R. (Dept. Medicine, Mount Sinai Sch. Medicine, New York, NY 10029) Donovan, P.; Cuttner, J. *Lancet* 1(8016): 866; 1977.

The case of a 49-yr-old woman with polycythemia vera associated with increased fetal hemoglobin (HbF) is presented. The patient was admitted with splenomegaly, and a diagnosis of polycythemia vera was made. HbA was the dominant Hb, but the proportion of HbF was 28%-32%. Acid elution was used to determine the heterogeneous distribution of HbF. Polycythemia vera can now be added to the growing number of blood diseases that are associated with acquired disorders of Hb synthesis. The increased HbF might be a marker produced by the clone of erythroid precursors responsible for the polycythemic state. (7 refs.)

- 77-1717 A Case of Small-Cell Sezary's Syndrome with Null-Cell Features.** (Eng.) Goldstone, A. H. (Dept. Haematological Medicine, Univ. Cambridge, Sussex, England) Cawley, J. C.; Roberts, S. O.; Leventine, A.; Barker, C. R. *J Clin Pathol* 29(9): 848-851; 1977.

The case history of a 73-yr-old man with Sezary's syndrome (SS) is presented. The patient's SS cells lacked surface-marker characteristics of both T- and B-cells, and only 3.5% of his mononuclear cells formed E rosettes with 2-aminoethylisothiuronium bromide-treated sheep RBC. The clinical and hematological features presented by the patient were those of small cell SS. (11 refs.)

- 77-1718 Negative Anion Gap in a Young Adult with Multiple Myeloma.** (Eng.) Gumprecht, T. (Dept. Medicine, Div. Clinical Pathology, Univ. California, San Diego, La Jolla, CA) O'Connor, D. T.; Rearden, A.; Wolf, P. L. *Clin Chem* 22(11): 1920-1921; 1976.

The case history of a 23-yr-old man with multiple myeloma is presented. The patient presented with complaints of progressive pleuritic chest pain, headaches, weakness, and wt loss of 4 mo duration. The patient was found to have a negative anion gap of 2 millimole/liter with marked asymptomatic hyponatremia. The myeloma protein, which acts as a cation at physiological pH, was thought to be responsible for the negative anion gap. The occurrence of the anion gap in multiple myeloma is discussed. (11 refs.)

- 77-1719 Lymphatic Dissemination of Bone and Soft Tissue Sarcomas. A Lymphographic Investigation.** (Eng.) Tallroth, K. (The First Dept., Inst. Diagnostic Radiology, Meilahti Hosp., Helsinki, Finland) *Acta Radiol [Suppl] (Stockh)* (349): 7-84; 1976.

Lymphographic investigations were performed on 132 patients with bone (61) and soft tissue (71) sarcomas to determine the incidence of lymphatic dissemination and the time relation between lymphatic and hematogenic dissemination in different sarcomas. Special lymphographic features of sarcoma metastases, the number of lymph node metastases detected solely by lymphography, and the value of follow-up films and repeat lymphography in detecting new metastases and assessing treatment were also studied. Of the 61 patients with primary bone sarcomas, 28 showed lymphatic involvement. Lymphatic dissemination was demonstrated in 16; of these, 13 were to regional lymph nodes, 8 to distant nodes, and 5 to both. Lymphatic involvement was noted in 40 of the soft tissue sarcoma patients, and in 24 lymphatic dissemination to distant parts of the body was seen. All 24 had metastases in regional nodes, and 8 had metastases to distant nodes. The highest frequency of lymphatic spread in the bone sarcomas was in patients with reticulosarcoma. In soft tissue

sarcomas, rhabdomyosarcoma had the highest frequency of lymphatic spread. Half of the cases of Ewing's sarcoma and reticulosarcoma had evidence of lymphatic spread before blood-borne metastases were detected. In osteosarcoma lymphatic dissemination always occurred after hematogenic spread. In synovial sarcoma, rhabdomyosarcoma, and neurogenic sarcoma, the first dissemination was more frequently lymphatic than hematogenic. The lymph node metastases of reticulosarcoma of bone had lymphographic appearances similar to those found in reticulosarcoma of soft tissue or lymph node origin. Lymph node metastases of the other sarcomas showed no special features. Of the 40 cases of lymph node metastases, 73% were first revealed by lymphography. Follow-up lymphographies were performed in 33 patients with lymph node metastases. In 8, new metastases were found, and in 13 previous metastases were found to have progressed. Apparent diminution of metastases was observed in 13 cases, indicating favorable response to radiation therapy. Nomenclature and classification of sarcomas, lymphographic appearance and changes due to treatment, and lymphographic diagnosis of metastases were reviewed. (222 refs.)

- 77-1720 Osteosarcoma in Siblings: Report of Two Cases.** (Eng.) Miller, C. W. (Dept. Orthopedics and Rehabilitation, Univ. Virginia Sch. Medicine, Charlottesville, VA 22901) McLaughlin, R. E. *J Bone Joint Surg [Am]* 59-A(2): 261-262; 1977.

Case reports are presented for two sisters who developed osteosarcoma of the right femur at age 15 yr and 17 yr, respectively. The patients' mother and maternal aunt had died of breast cancer, and their maternal grandmother, of colon carcinoma. (9 refs.)

- 77-1721 Metastatic Characteristics of Murine Neuroblastoma: A Model for the Human Disease (Meeting Abstract).** (Eng.) Buck, B. E. (Children's Hosp. Philadelphia, Philadelphia, PA 19104) McAlack, R. F.; Schlesinger, H.; Hicks, N.; Hummeler, K. *Fed Proc* 36(3): 1086; 1977. (no refs.)

- 77-1722 Direct Resorption of Bone by Human Monocytes.** (Eng.) Mundy, G. R. (Dept. Medicine, Univ. Connecticut Health Center, Farmington, CT 06032) Altman, A. J.; Gondek, M. D.; Bandelin, J. G. *Science* 196(4294): 1109-1111; 1977.

Stimulation of the release of bone mineral and matrix from killed long bones of fetal rats by cultured human peripheral blood monocytes was investigated. When human mononuclear cells, from which neutrophils were separated by Ficoll-

Hypaque sedimentation, were cultured with killed bones for 5-8 days, there was an increase in ^{45}Ca and ^3H -proline release from the bones compared with paired bones cultured without cells. The greatest increase in mineral release occurred between days 4 and 8 of culture. The mononuclear cells were much more effective in resorbing killed bone than the nonadherent population. Parathyroid hormone, osteoclast activating factor, $1\alpha,25$ -dihydroxycholecalciferol, and prostaglandin- E_2 did not increase mineral release from killed bones stimulated by mononuclear cells during an 8-day period. In a separate experiment, salmon calcitonin (100 milliunits/ml medium) did not inhibit bone resorption stimulated by mononuclear cells. However, cortisol (10^{-6}M) significantly inhibited ^{45}Ca release during 8 days of culture. The effects were inhibited by cortisol, but they were altered by hormones that normally stimulate osteoclastic bone resorption. There was no evidence of morphologic differentiation of the monocytes into osteoclasts during bone resorption. (19 refs.)

- 77-1723 Distribution Pattern of Metastatic Bone Disease. A Need for Total Body Skeletal Image.** (Eng.) Krishnamurthy, G. T. (Building 300, Room GN-87, Veterans Admin. Wadsworth Hosp. Center, Los Angeles, CA 90073) Tubis, M.; Hiss, J.; Bland, W. H. *JAMA* 237(23): 2504-2506; 1977.

A study was made to determine the general distribution of metastatic bone disease, its dependence on the primary tumor, the importance of elevated serum alkaline phosphatase (AP) levels, and whether routine study of the appendicular skeleton is warranted. The distribution of metastatic bone lesions was analyzed in 62 patients (33-87 yr old, mean 64 yr) with histologically proved cancer by $^{99\text{m}}\text{Tc}$ imaging. Primary tumor sites were breasts (19), prostate (12), lung (11), and kidney (5); the rest had miscellaneous cancers. A total of 403 bone lesions were detected (av 6.5/patient), the majority (60.3%) in the axial skeleton, the remainder in the appendicular skeleton (including ribs, sternum, and clavicle). Excluding lesions of the ribs and clavicles, 11.1% of the total were detected in the upper and lower extremities, regions not ordinarily included in routine bone imaging. In lung tumor patients, 43% of the total lesions were in the ribs, compared to 12.7% in breast tumor patients. The serum AP level correlated with the total number of lesions in 23 patients, but in 9 with definite evidence of bone lesions, the AP level was normal. Serum AP level is concluded to be a poor indicator of early bone metastases. (12 refs.)

- 77-1724 Von Recklinghausen's Disease.** (Eng.) Banyai, A. L. (No affiliation given) *Chest* 71(3): 365; 1977.

The manifestations of von Recklinghausen's disease (RD) are reviewed with emphasis on the sites involved by neurofibromas and on bone and joint changes. Malignant transfor-

mation of neurofibromas may occur in 2-16% of patients with RD. (6 refs.)

- 77-1725 New Cutaneous Phenotype in Familial Malignant Melanoma (Letter to Editor).** (Eng.) Frichot, B. C. (Dept. Dermatology and Preventive Medicine, Creighton and Nebraska Health Foundation, Omaha, NB 68178) Lynch, H. T.; Guirgis, H. A.; Harris, R. E.; Lynch, J. F. *Lancet* 1(8016): 864-865; 1977.

An extended kindred showing an excess of cutaneous malignant melanoma and associated malignant neoplasms was studied. In this family, the mother with cutaneous malignant melanoma and her three cancer-free children manifested the same cutaneous phenotype: large moles, from 1 to 200 per patient, that are reddish brown to pink in color and with an irregular border. Histologically, they show a cellular dermal component and a bizarre intraepidermal pattern. In a second family studied, both parents had adenocarcinoma of the colon, one sister had cutaneous malignant melanoma, another sister had intraocular melanoma, and a brother had Bowen's disease of the back. The cutaneous phenotype in the children and adults of this family was characterized by a distinctive freckling pattern and dryness, features similar to xeroderma pigmentosum (XP). These observations suggest that in some melanoma-prone kindreds, invaluable clues for recognizing susceptibility to this disease and certain associated malignant neoplasms are available. Recognition of the XP-like phenotype in familial malignant melanoma is consistent with the genetic heterogeneity in this disease. (7 refs.)

- 77-1726 Angiogenesis and Wound Healing (Meeting Abstract).** (Eng.) Rettura, G. (Albert Einstein Coll. Medicine, Bronx, New York, NY 10461) Seifter, E.; Barbul, A.; Levenson, S. M. *Fed Proc* 36(3): 1087; 1977. (no refs.)

- 77-1727 Altered Schistosome Granuloma Formation in Nude Mice (Meeting Abstract).** (Eng.) Byram, J. E. (Peter Bent Brigham Hosp., Harvard Medical Sch., Boston, MA 02115) von Lichtenberg, F. *Fed Proc* 36(3): 1057; 1977. (no refs.)

- 77-1728 The Significance of the Vertebral Venous (Batson's) Plexus in Metastatic Spread (Meeting Abstract).** (Eng.) Vider, M. (Radiotherapy Dept., Temple Univ. Hosp., Philadelphia, PA) Maruyama, Y. *Int J Radiat Oncol Biol Phys* 1(Suppl 1): 37; 1976. (1 ref.)

- 77-1729 The Significance of Free Blood in Liquid and Solid Tumours.** (Eng.) van den Brenk, H. A. (Richard Dumbleby Dept. Cancer Res., St. Thomas's Hosp. Medical Sch., London SE1 7EH, England) Crowe, M.; Kelly, H.; Stone, M. G. *Br J Exp Pathol* 58(2): 147-159; 1977.

Microvascular changes induced in rats by liquid (ascites) and solid growth of W256 and Y-P388 tumor cells were observed after perfusion of the vasculature with India ink. In both tumors free blood was present due to diapedesis of erythrocytes through tips of capillary sprouts which grow when neovascularization (angiogenesis) occurs in response to any suitable (non-neoplastic or neoplastic) stimulus. Ascites growth of these tumors induced profuse sprouting from the peritoneal capillaries, causing "bleeding". Local preirradiation of the peritoneal vasculature with X-rays before inoculation of rats with the tumours inhibited sprouting and subsequent free blood. Similar angiogenesis with bleeding did not occur following inoculation with an allogeneic tumor in rats which had been previously immunized against the tumor. LI tumor cells (tumor cells lethally irradiated in vitro to destroy their proliferative integrity, but which remain metabolically active although lethal radiation has destroyed proliferative integrity) also induced sprouts to grow in close proximity to the implanted LI cells; heat-killed tumor cells caused no sprouting. The findings indicated that leakage of blood from the microvasculature of tumors normally accompanies growth of capillary endothelium. It is suggested that the neovascularization occurring in tumors parallels that which occurs in non-neoplastic growth, such as growth of granulation tissue. (25 refs.)

- 77-1730 Tumor Cell Locomotion--A Factor in Metastasis Formation? Influence of Cytochalasin B on a Tumor Dissemination Pattern.** (Eng.) Hagmar, B. (Dept. Pathology, Sundsvalls Hosp., Sundsvall, Sweden) Ryd, W. *Int J Cancer* 19(4): 576-580; 1977.

The influence of cytochalasin B (CB)-induced paralysis on the pattern of tumor cell dissemination was studied. TA3 ascites tumor cells were treated with either 1 or 10 µg/ml CB and then injected into A/Sn mice either iv or sc at doses of 10^4 , 10^5 , and 10^6 cells iv and 10^2 and 10^3 cells sc. Pretreatment with 1 µg/ml CB did not alter the sc or iv transplantability of the TA3 cells. Pretreatment with 10 µg/ml CB consistently increased the incidence and number of extrapulmonary tumor takes from iv administered cells. Sc transplantability, however, was not affected. Animals given cells pretreated with CB for 5 min lived longer than those given cells pretreated for 60 min. It was concluded that cell paralysis is compatible with tumor cell survival in the blood and that it may even increase tumor development by promoting transcapillary passage. The importance of cell mobility and cell surface topography for tumor cell migration in the vessels is discussed. (21 refs.)

- 77-1731 Morphological and Biochemical Studies on Adenoid Cystic Carcinoma Cells (Meeting Abstract).** (Eng.) Takeuchi, J. (Dept. Pathology, Sch. Medicine, Fujita-Gakuen Univ., Japan) Sobue, M.; Katoh, Y.; Yoshida, M.; Esaki, T.; Miura, K. *Jpn J Cancer Clin* 23(3): 163-166; 1977. (no refs.)

- 77-1732 Ten Cases of Multiple Malignant Tumors.** (Fre.) Pieron, R. (Hopital Tenon, 75970 Paris Cedex 20, France) Blanche, J. M. *Sem Hop Paris* 53(6): 369-375; 1977.

The literature on multiple malignant neoplasms is reviewed, and 10 case histories are presented. Multiple malignancies are defined as those with a different or analogous histology affecting different organs; the topography of the organs and the time interval rule out metastases. There were four chronic lymphoid leukemias (associated in two patients with bronchogenic carcinomas and in two patients with gastric adenocarcinomas) and six double cancers. The double cancers included three bronchogenic carcinomas associated, respectively, with a carcinoma of the rectum, a carcinoma of the prostate, and a bronchogenic adenocarcinoma; two colonic adenocarcinomas, one bifocal and associated with polycythemia and a cutaneous carcinoma and the other with a bladder carcinoma; and a breast adenocarcinoma associated with a gastric cancer. The histopathology of the tumors was confirmed in all cases. The pathogenesis of multiple malignancies is discussed, particularly from the aspects of immunodepression and genetics. (44 refs.)

- 77-1733 Carcinoma in the Defunctionalized Bladder: Report of a Case and Review of the Literature.** (Eng.) Garvin, D. D. (Urology Service, Dept. Surgery, Wilford Hall United States Air Force Medical Center, Lackland Air Force Base, TX) Weber, C. H.; Polsky, M. S. *J Urol* 117(5): 669-670; 1977.

The case history of a 68-yr-old man with carcinoma in a defunctionalized bladder is presented. The patient presented with a long history of recurrent urinary tract infections, and the left kidney had been removed 25 yr earlier. Cystography showed right vesicoureteral reflux, and cystoscopy demonstrated evidence of chronic bladder inflammation with a generalized erythematous and edematous mucosa, as well as areas of leukoplakia. Biopsy showed squamous metaplasia with acute and chronic inflammation. A right ureteral reimplantation was performed followed by a cutaneous ureterosotomy. Three years later the patient was readmitted because of passage of blood per urethram. Multiple biopsies revealed a highly anaplastic, superficially invasive, transitional cell carcinoma, and a cystourethrectomy was performed. There was no evidence of perivesical extension or lymph node involvement. Recovery was uneventful. (2 refs.)

- 77-1734 Renin-secreting Benign "Juxtaglomerular Cell" Tumor of the Kidney. Microscopic and Electron Microscopic Study.** (Fre.) Baldet, P. (Laboratoire d'Anatomie pathologique, Centre Gui de Chauliac, 34059 Montpellier, France) Mimran, A. *Ann Anat Pathol (Paris)* 22(1): 21-40; 1977.

The literature on benign renin-secreting tumors of the kidney is reviewed, and the case report of a 22-yr-old woman is presented. These tumors are a rare cause of arterial hypertension, and only nine case histories have been published. The young woman developed visual difficulties in the seventh month of pregnancy, and an arterial hypertension of 220/110 and diffuse bilateral retinal hemorrhages were observed. A normal infant was delivered, but blood pressure failed to respond to several antihypertensive drugs, such as dihydralazine, propranolol, methyldopa, and chlorothiazide. The ocular lesions progressed, almost to bilateral optic atrophy. When blood pressure fell after administration of the angiotensin antagonist 1-sarcosine-8-alanine angiotensin and a high level of plasma renin was discovered, a renin-secreting tumor was suspected. Renal angiography revealed a round avascular image in the superior pole of the right kidney. The tumor was easily enucleated at surgery, and blood pressure levels fell to normal, as did plasma renin, K, and aldosterone. The tumor was highly vascularized and composed of epithelial cells similar to those observed in the normal juxtaglomerular apparatus. Of significant diagnostic value was the massive infiltration of mastocytes. Ultrastructural study clearly differentiated the secretory cells from the smooth muscle fibers of the blood vessels. Other types of renin-secreting tumors are discussed briefly. (42 refs.)

- 77-1735 Multiple Adenomatous Neoplasms Arising in Columnar-Lined (Barrett's) Esophagus.** (Eng.) McDonald, G. B. (Dept. Medicine and Pathology, Seattle Veterans Admin. Hosp., 4435 Beacon Avenue South, Seattle, WA 98108) Brand, D. L.; Thorning, D. R. *Gastroenterology* 72(6): 1317-1321; 1977.

A 62-year-old man had multiple polypoid masses in the esophagus. Exfoliative and brush cytological studies were positive for adenocarcinoma. Esophageal resection showed a lining of columnar epithelial cells which were focally hyperplastic, forming polypoid masses. Atypical epithelial cell changes, ranging from dysplasia to focal carcinoma, appeared in both the masses and the mucosa between them. These findings reinforce the concept that the Barrett's (columnar) epithelium is a premalignant lesion deserving periodic screening. (44 refs.)

- 77-1736 Comparative Structural Analysis of Human Bronchiolo-Alveolar Carcinoma and Pulmonary Carcinoma of Sheep (Meeting Abstract).** (Eng.) Perk, K.

(Hebrew Univ. Jerusalem, Rehovot, Israel) *Isr J Med Sci* 13(3): 341; 1977. (no refs.)

- 77-1737 Ultrastructure of a Human Lung Cancer Transplantable and Inducing Granulocytopoiesis in Host Nude Mice (Meeting Abstract).** (Eng.) Akatsuka, A. (Div. Electron Microscopy Dept. Pathology, Tokai Univ. Sch. Medicine, Isehara, Kanagawa, Japan) Tamaoki, N. *Electron Microsc (Tokyo)* 25(3): 202; 1976. (no refs.)

- 77-1738 Pleural Calcification Due to Asbestosis and Associated Pathology (Study of 32 Cases).** (Fre.) Moigneteau, Ch. (Centre Hospitalier et universitaire de Nantes, Hopital Laennec, 44035 Nantes Cedex, France) Touzeau, P. Y.; Guillement, J. M. *Poumon Coeur* 33(2): 101-105; 1977.

Calcified pleural plaques were observed in 32 men (48-84 yr old, av, 60) who had been occupationally exposed to asbestos for an av of 27 yr. The delay between initial exposure and appearance of the plaques was long, an av of 32 yr. The plaques were usually diffuse, involving the parietal and diaphragmatic pleura in 16 patients and, in addition, the mediastinal pleura in 8. Smoking habits were obtained for 28 men: 22 were smokers, 5 heavy smokers, and 6 were nonsmokers. Malignant tumors were associated with the plaques in four patients (2 pleural mesotheliomas, 1 lung cancer, and 1 liver metastasis with primary site unknown) at the time of initial diagnosis, and bronchogenic carcinoma developed subsequently in two patients. Of the 32 men, 19 were followed for at least 2 yr. The 3 patients with lung or pleural malignancies at time of initial discovery of plaques died, a serofibrinous pleurisy developed in 1 patient, and 13/19 did not experience any further complications associated with the plaques. (28 refs.)

See also:

- * (Rev.): 77-1212, 77-1228, 77-1230, 77-1231, 77-1242, 77-1243.
- * (Chem.): 77-1329, 77-1334, 77-1356, 77-1369, 77-1379, 77-1391, 77-1392, 77-1393, 77-1394, 77-1399, 77-1416.
- * (Phys.): 77-1426, 77-1429, 77-1433, 77-1436, 77-1451, 77-1458, 77-1459, 77-1460, 77-1462.
- * (Viral): 77-1472, 77-1525, 77-1534, 77-1537, 77-1538, 77-1554, 77-1556.
- * (Immun.): 77-1600, 77-1615, 77-1621, 77-1667, 77-1674, 77-1686.
- * (Epid.-Biom.): 77-1741, 77-1742, 77-1747, 77-1750, 77-1759, 77-1763.

EPIDEMIOLOGY AND BIOMETRY

- 77-1739 **Recent Time-Trends of Age-specific Death Rates for Breast Cancer: Quebec and Other Provinces, 1965 Through 1974.** (Eng.) Fabia, J. (Faculte de medecine, Universite Laval, Quebec, PQ G1K 7P4, Canada) Bernard, P. M.; Hill, G. *Can Med Assoc J* 116: 1135-1138; 1977.

Analysis of Canadian breast cancer mortality rates for the period 1965 through 1974 showed that the age-specific death rates decreased among middle-aged women, especially at ages 40-49 yr, in Quebec, the Maritimes, and the Prairies, but not in Ontario or British Columbia. In women < 35 yr, the mortality generally increased; in women aged 60-64 yr there was little change except in the Prairies, where the rate increased. The trends apparently reflect changes in incidence rather than in case fatality. Some but not all of the trends can be explained by changes in fertility over the past 50 yr. As in the US and northern Europe, breast cancer incidence and mortality rates in Canada are five to six times higher than in most Asian countries. Diet may therefore be involved in the etiology of breast cancer. (33 refs.)

- 77-1740 **Age-specific Incidence of Cancer of the Endometrium, Ovary and Breast in the United Kingdom and the United States.** (Eng.) Anthony, H. M. (Dept. Experimental Pathology and Cancer Res. Univ. Leeds, Sch. Medicine, Leeds 2, England) *Int J Immunol* 5(3): 231-236; 1976.

Incidence data for cancer of the endometrium, ovary, breast, and cervix from cancer registries in Birmingham, England, and Connecticut were compared for 1960-1962 and 1963-1965/66. The incidence of cancer of the endometrium, ovary, and breast in Connecticut was higher than that in Birmingham. In each case, the menopausal dislocation in the age-specific incidence plot of the Birmingham data was not seen in the plot for Connecticut. The incidence of cancer of the cervix uteri was similar in Birmingham and Connecticut. This is in keeping with epidemiological data linking cervical cancer with a genital transmission pattern. For endometrial cancer, the difference correlates with differences between the two countries in the use of estrogen replacement therapy, which was recently implicated in the etiology of endometrial cancer. The similarity in the pattern for ovarian and breast cancer and the changing pattern of breast cancer incidence in Birmingham suggest a similar etiological effect. (17 refs.)

- 77-1741 **An Epidemiological Study of Cancer of the Ovary.** (Ger.) Lau, H. U. (Frauenklinik des Bereiches Medizin--Charite, DDR-104 Berlin, Tucholskystr. 2, E. Germany) Petschelt, E.; Pochls, H.; Unger, H. H.; Zegenhagen, V. *Arch Geschwulstforsch* 47(1): 57-66; 1977.

A group of 149 patients with ovarian carcinomas was compared to an age-matched (26 to 80 yr) group of women from the general population. There was no statistically significant difference between the two groups with respect to the presence of diabetes mellitus (4.7% of patients; 8.1% of controls); earlier treatment with hormones, such as estrogens, androgens, gestogens, and gonadotropins, alone or in combination; certain extragenital diseases; benign gynecologic diseases (eg, uterine myomas); or disturbances of the menstrual cycle, although 14/149 patients suffered from acyclic bleeding compared to 7/149 controls. There was also no difference in age at menarche or menopause, number of pregnancies, previous irradiation, blood group, or nicotine consumption. The family histories of the patients and controls showed no familial tendency to ovarian carcinoma. There was a statistically significant difference between patients and controls in two areas: 10.1% of the patients were unmarried compared to 4.7% of the controls (the "married" classification included women who were separated or widowed), and 49% of the patients suffered from hypertension (blood pressure > 160/95 mm Hg) compared to 38.2% of the controls. (38 refs.)

- 77-1742 **Incidence of Malignancy in Jewish Women with Postmenopausal Bleeding.** (Eng.) Caspi, E. (Dept. Obstetrics and Gynecology, Asaf Harofe Government Hosp., Zerifin, Israel) Perpinial, S.; Reif, A. *Isr J Med Sci* 13(3): 299-304; 1977.

A survey of Jewish women admitted to an Israeli hospital for postmenopausal bleeding (associated with a relatively high incidence of malignancy) during 1962-74 is presented. Of 397 cases, 13.8% were due to malignancy: 34 women with endometrial carcinoma, 11 with cervical carcinoma, five with ovarian carcinoma, four with uterine sarcoma and one with vaginal sarcoma. In 86% of cases, benign pathological states were found, 42.8% associated with atrophic endometrium. An active endometrium was found in 56 patients (14%); in two of these the endometrium was secretory. Estrogen therapy was not an important causative factor in these cases. The low incidence of malignancy seems to be due to the fact that cervical carcinoma is less common among Jewish women. Invasive epidermoid carcinomas of the cervix accounted for 20% of the malignancies, indicating the need for a cytologic screening program in Israel. (20 refs.)

- 77-1743 **Vaginal and Cervical Cancers and Other Abnormalities Associated with Exposure In Utero to Diethylstilbestrol and Related Synthetic Hormones (Letter to Editor).** (Eng.) Adam, E. (Dept. Epidemiology and Obstetrics-Gynecology, Baylor Univ., Coll. Medicine, 1200 M. D. Anderson St., Houston, TX 77025) Decker, D. G.; Herbst,

A. L.; Noller, K. L.; Tilley, B.; Townsend, D. E. *Cancer Res* 37(4): 1249-1251; 1977.

The association between gynecologic cancers and nonmalignant lesions and in utero exposure to diethylstilbestrol (DES) and related hormones is discussed on the basis of data available at the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females in Chicago. Recommendations are made for the management of young women exposed to DES-type drugs. More than 500 subjects with documented in utero exposure have been identified by the four institutions participating in the NCI DES and Adenosis Project. (14 refs.)

77-1744 Benign Breast Disease and Oral Contraceptive Use. (Eng.) Janerich, D. T. (Cancer Control Bureau, New York State Dept. Health, Albany, NY 12237) Glebatis, D. M.; Dugan, J. M. *JAMA* 237(20): 2199-2201; 1977.

The history of oral contraceptive use in women with a clinical diagnosis of benign breast disease was studied in 1,230 randomly selected women of childbearing age. A total of 73 women reported having had benign breast disease. These women used birth control pills for a shorter av time than women who did not have this condition. A significant portion of the women with benign breast disease indicated that they had been advised to discontinue pill use for breast-related reasons. A survey of upstate New York physicians showed that 33% considered benign breast disease as a potential contraindication for starting oral contraceptive use, and 47% thought the development of benign breast disease to be a potential contraindication for continuing oral contraceptive use. It cannot be concluded that oral contraceptive usage protects against benign breast disease. (11 refs.)

77-1745 Chromosomes, the Oral Contraceptive and Possible Breast Cancer (Meeting Abstract). (Eng.) Smith, N. (Tissue Culture and Cytogenetics Unit, Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England) Bishun, N. P.; Williams, D. C. *Mutat Res* 46(3): 236-237; 1977. (no refs.)

77-1746 Is There Any Bimodality of the Age Distribution of Male Mammary Cancer? (Fre.) Brunet, M. (Section Cancer de la D.R.M.S., I.N.S.E.R.M., 44, Chemin de Ronde, F 78110 Le Vesinet, France) Hucher, M.; Boutros, F.; Berlie, J. *Rev Epidemiol Sante Publ* 24(5): 405-413; 1976.

The age distribution of men with breast cancer was determined from three sources of material: (1) 512 cases registered from 1955 to 1968 at the Permanent Cancer Information

Center in Paris, which collects information on cancer patients treated at centers throughout France; (2) 854 cases from a UICC publication reporting the incidence of cancer in Europe (cases from France were excluded), the US, and Asia; (3) 460 deaths attributed to cancer of the male breast in study on cancer mortality in France from 1968 to 1970. The patients in Groups 1 and 2 could be divided into two subgroups: 246 patients who had a mean age of 47 yr and 1,100 patients who had a mean age of 66.5 yr. Mortality (Group 3) also fell into two distribution curves, one with a mean of 48 yr and one with a mean of 73.5 yr. The younger age group may represent patients with various testicular dystrophies, which increase the risk of cancer. (14 refs.)

77-1747 Cancer of the Penis in Denmark 1942 to 1962 (511 Cases). (Eng.) Jensen, M. S. (Frihedsvej 14, DK-4700 Naestved, Denmark) *Dan Med Bull* 24(2): 66-72; 1977.

According to the Cancer Register of Denmark, there were 511 cases of cancer of the penis (CP) in the country from 1942 to 1962. The av age at diagnosis was 63.7 yr (range 28-95). The frequency was higher than expected in the middle class, but the frequency was no higher than expected in the lower classes. Phimosis, a possible predisposing factor to CP, occurred significantly more often among the cancer patients (53%) than among men in general (3-8%). This was also true for syphilis: the occurrence was 9.4% compared to 3.6% in a group of paired control subjects. A precancerous condition preceded CP in only 7.6% of the patients. Tumors of the prepuce had a better prognosis than those originating from other sites, and the prognosis for ulcerative types was poorer than that for the exophytic and scirrhous types. Most of the CP were squamous cell carcinomas (96.6%). There was a significant correlation between histological grade and prognosis. Of the 511 patients, 389 were dead at the time of the survey; CP was the direct cause of death in 154 and the indirect cause in 19. There were 15 deaths within one mo of the operation, corresponding to an operative mortality of approx 3% and 55.5% of the 389 deaths were caused by diseases which could not be related to CP. Treatment was usually surgical (circumcision, partial and total amputation, and orchiectomy), and the degree of surgery was dictated by the location and stage of disease. Adjuvant radiotherapy did not produce results superior to those of surgery alone. At follow-up times of 7-27 yr in 119 surviving patients, it was found that they did relatively well psychologically, sexually, and socially. (28 refs.)

77-1748 Malignant Tumors of the Testis (Letter to Editor). (Eng.) Petersen, G. R. (State of California Dept. Health, 2151 Berkeley Way, Berkeley, CA 94704) Lee, J. A.; Weathersby, M. E. *J Natl Cancer Inst* 58(2): 173; 1977.

Occupational mortality data in England and Wales indicated

that professional and administrative workers die at an earlier age than their unskilled counterparts from malignant tumors of the testis. These findings are in agreement with those of a previous study in California, in which an acceleration of the neoplastic process in the testis was associated with affluence. (5 refs.)

- 77-1749 **Screening for Liver Disease in Vinyl Chloride Workers.** (Eng.) Lee, F. I. (Dept. Medicine, Victoria Hosp., Blackpool, England) Harry, D. S.; Adams, W. G.; Litchfield, M. *Br J Ind Med* 34(2): 142-147; 1977.

The results of screening for liver disease in workers exposed to vinyl chloride are presented. There was no significant difference in liver function tests of workers exposed to vinyl chloride as compared to men in the same factory who were not exposed. However, four exposed workers had splenomegaly. (21 refs.)

- 77-1750 **Cytogenetic Investigations on Lymphocytes from Workers Exposed to Vinyl Chloride.** (Eng.) Leonard, A. (Lab. Genetics, Dept. Radiology, C.E.N.-S.C.K. B 2400 Mol, Belgium) Decat, G.; Leonard, E. D.; Lefevre, M. J.; Decuyper, L. J.; Nicaise, C. *J Toxicol Environ Health* 2(5): 1135-1141; 1977.

Eleven male workers from the polymerization department of a VC factory, seven people employed in the laboratory of another VC plant, and ten controls from outside the factory environment were examined for the presence of chromosome aberrations in blood lymphocytes and these cytological findings were viewed in light of the occupational and medical histories of the subjects. Most of the workers from the polymerization department had chromosome anomalies such as fragments, rings, translocations, and dicentrics. However, since these workers received frequent radiographs of the hands, feet, vertebral column and digestive tract, it is impossible to determine whether these chromosome anomalies result from vinyl chloride exposure or from diagnostic exposure to ionizing radiations. It is concluded that the risk of significant increase in chromosome aberrations due to occupational exposure to VC seems small and that present working conditions in VC plants are within acceptable safety limits. (17 refs.)

- 77-1751 **Genetic Study on PVC Workers (Meeting Abstract).** (Eng.) Czeizel, A. (Natl. Inst. Hygiene, Budapest, Hungary) Szentesi, I.; Hornyak, E.; Ungvari, G.; Bogнар, Z.; Timar, M. *Mutat Res* 46(3): 215-216; 1977. (no refs.)

- 77-1752 **Acrylonitrile Linked to Cancer in Workers.** (Eng.) Anonymous (No affiliation given) *Chem Eng News* 55(22): 6; 1977.

Due to acrylonitrile's (AN) structural similarity to vinyl chloride, a study was conducted on 470 AN workers at a textile fibers plant in Camden. There were 16 cases of cancer reported, all occurring in workers initially exposed to AN during the startup of the plant in 1950-52. This preliminary study does not provide definitive evidence of the carcinogenicity of AN in man. Follow-up studies and investigations at other plants are planned. (no refs.)

- 77-1753 **Effects of Pesticide Residues on Blood Pressure (Meeting Abstract).** (Eng.) Budy, A. M. (Pacific Biomedical Res. Center and Dept. Genetics, Univ. Hawaii, Honolulu, HI 96816) Rashad, M. N.; Mi, M. *Fed Proc* 36(3): 1008; 1977. (no refs.)

- 77-1754 **Measurement of Some Potentially Hazardous Materials in the Atmosphere of Rubber Factories.** (Eng.) Nutt, A. (Dunlop Res. Centre, Birmingham, England) *Environ Health Perspect* 17: 117-123; 1976.

The measurement of chlorinated monomers in polyvinyl chloride (PVC) and polychloroprene, and the measurement of benzopyrene (BP) in factory air, particularly in the tire industry, are outlined. BP is present in trace quantities in the mineral oils and carbon blacks used in tire manufacture. Measurements taken daily over a 2-yr period showed no significant concentrations of BP in the atmosphere within the tire plant as compared to an outside air station. (6 refs.)

- 77-1755 **Frequency of Prenatal X-Ray Examination and Radiation Risks in Japan.** (Eng.) Kitabatake, T. (Dept. Radiology, Sch. Medicine, Niigata Univ., Niigata 951, Japan) Sato, T.; Takeuchi, S. *J Radiat Res (Tokyo)* 17(3): 204-210; 1976.

The frequency of prenatal x-ray examination in 1,701 parturient women was assayed in 19 Japanese hospitals in 1974. A total of 1,231 women were not x-rayed, but 470 were. Maternal x-ray studies were slightly more frequent in the primipara than the multipara, but no statistically significant difference was recognized. The fetus received an av of 202 millirads of radiation from the prenatal x-ray examinations. Based on these data, approx 6.5 leukemias could be induced per year by maternal x-ray, corresponding to approx 1% of the leukemias in the same generation. Approx 82% of the fetal dose was contributed from prenatal pelvimetric studies made mainly after the 10th month; chest examination was frequent

in the 3rd-6th months of gestation. When the pelvimetric cases only are considered, fetal radiation dose is estimated as approx 1,800 millirads in the upper limits, which may produce approx nine times the radiation risk compared with that in the general population of children. (13 refs.)

- 77-1756 How Safe Is Nuclear Power? (Letter to Editor).** (Eng.) Coulter, J. R. (Inst. Medical and Veterinary Science, P.O. Box 14, Rundle St., Adelaide, South Australia, Australia 5000) *Med J Aust* 1(16): 603-604; 1977.

The claim that there is no evidence of injury among radiation workers at a nuclear fuel reprocessing plant is disputed. The true incidence of leukemia and of actual vs expected deaths among plutonium workers may have been disguised by grouping these workers with a much larger group of unexposed workers. Moreover, no follow-up records are available for radiation workers who have left the industry. (2 refs.)

- 77-1757 An Investigation of Occupational Exposure on Taiwan (1973-1975).** (Eng.) Weng, P. S. (Health Physics Section, Natl. Tsing Hua Univ., Hsinchu, Taiwan 300) Wang, C. L. *Health Phys* 31(6): 513-516; 1976.

Data on the occupational exposure to ionizing radiation on Taiwan from 1973 to 1975 is analyzed. During this 3-yr period, the annual dose equivalent was below 500 millirem (roentgen equivalent man) in 91% of the radiation workers. The annual dose exceeded 5 rem in less than 0.4% of the workers. The total av man-rem was less than 363 man-rem annually. Technical assistants in the medical fields represented the majority (60.0%) of the occupationally exposed personnel on Taiwan. (9 refs.)

- 77-1758 Cancer and Hair Dyes: Reply to Dr. Shafer's Letter (Letter to Editor).** (Eng.) Menkart, J. (Clairol Inc., 2 Blachley Road, Stamford, CT 06902) Lanman, B. M. *NY State J Med* 77(3): 444; 1977.

There is no evidence that hair dye preparations cause cancer, teratogenic or reproductive abnormalities in either humans or experimental animals. The increase in the number of women using hair dyes in the past 20 yr has not been accompanied by a corresponding increase in the number of cases of breast cancer. (1 ref.)

- 77-1759 Hepatic Angiosarcoma Within a Small Geographic Area (Letter to Editor).** (Eng.) Smithson, W. A. (Mayo Clinic, Rochester, MN) Elliott, S. C. *JAMA* 237(20): 2189; 1977.

The case history of a 13-yr-old boy with angiosarcoma involving the spleen, liver, and peritoneum is presented. The boy lived within 426 kilometers (km) of Marshfield, Wisconsin. Four cases of hepatic angiosarcoma occurring within 224 km of Marshfield were reported previously. The boy was operated on for abdominal pain, and numerous tumor nodules were found attached to the bowel, in the greater omentum, the gastocolic ligament, and at the tail of the pancreas. The spleen had been removed several months earlier and was found to contain angiosarcoma. Treatment was with multiple chemotherapeutic agents. The boy died a short time later. The occurrence of this rare tumor in a 13-yr-old boy from an area where four such tumors have been reported is significant. If a common etiologic agent exists, it may have a shorter latency period than thorium dioxide, arsenic, or polyvinyl chloride, which have latency periods of about 20 yr. The area should be surveyed for other cases and for possible environmental causes. (1 ref.)

- 77-1760 Some Characteristics of Mozambican Shangaans with Primary Hepatocellular Cancer** (Eng.) Kew, M. C. (Dept. Medicine, Johannesburg Hosp. Johannesburg, South Africa) Marcus, R.; Geddes, E. W. *Afr Med J* 51: 306-309; 1977.

Shangaans from Mozambique suffer the highest incidence of primary hepatocellular cancer (PHC) in the world: the incidence in men is 98.2/100,000, accounting for 65.5% of all cancers. Certain characteristics of 328 male Shangaans with PHC were compared with those of 163 male Shangaans with hepatomegaly from causes other than PHC and with those of 122 non-Shangaan blacks with PHC. The mean age of the Shangaan PHC patients was significantly less (33.4 yr) than that of the non-Shangaans (40 yr). α -Fetoprotein was detected in 71.4% of the Shangaan PHC group and 61% of the non-Shangaan group. Cirrhosis of the nontumorous part of the liver was seen at necropsy in 62% of the Shangaans and in 66% of the non-Shangaans. Hepatitis B virus surface antigen was detected in the sera of 60% of the Shangaans with PHC, 53.4% of the non-Shangaans, and 9% of the Shangaans without PHC. Discussion is made of the possible etiological role of hepatitis B virus in cirrhosis and PHC. The limited data regarding the dietary history of each of the groups did not point to any outstanding differences. All subjects ate groundnuts and cycad pips from an early age, and they could have been exposed to mycotoxins and cycasin. (22 refs.)

- 77-1761 Cancer in the Africans and Arabs of Zanzibar.** (Eng.) Chopra, S. A. (Commonwealth Dept. Health, Bendigo, Victoria, Australia) Chopra, F. S. *Int J Cancer* 19(3): 298-304; 1977.

A definite pattern was discerned among the cancers diagnosed histologically in Zanzibar during 1957-1962 and 1964-

1967. The total number of cancers diagnosed in all races over the period was 448 (73% African, 19% Arab, 4% Indian, and 4% others). The gradual increase in the number of cancers diagnosed from year to year (29 in 1957 to 60 in 1967) is best explained by the improvement in medical services. The sudden increase from 24 in 1959 to 48 in 1960 was mainly due to skin and female genital cancers in Africans. The Zanzibar Arab immigrants appear to have a decreased risk for esophageal and stomach cancers, which are common in other Arab countries. In both Africans and Arabs, cervical and skin cancers were the most common types, and skin cancer was mainly of the squamous cell type. Unlike the Zanzibar Africans, the Arabs had an elevated risk for Hodgkin's disease similar to that of the Middle East Arab population. The comparison of cancer patterns between Arabs and Africans makes it possible to study the possible role of genetic and environmental factors in carcinogenesis. (12 refs.)

77-1762 The Influence of Finite Observation Periods on Familial and Chronic Disease Epidemiology (Letter to Editor). (Eng.) Daitch, P. B. (Bio-Medical Engineering Center, Rensselaer Polytechnic Inst., Troy, NY 12181) Vianna, N. J. *J Natl Cancer Inst* 58(1): 9-10; 1977.

The influence of finite observation periods on familial and chronic disease epidemiology is discussed. In particular, two distinct methods used in familial studies of Hodgkin's disease are considered. Both methods require an objective source, such as a population-based tumor registry, to identify familial pairs with this disorder. Although all related pairs with Hodgkin's disease may be identified, statistical analyses are limited to first-degree relatives. A mathematical rationale for one method is presented, and certain aspects of the other are clarified. In one method the time interval between diagnosis and the proximity of the first-degree familial pairs are considered. Familial pairs are assigned to one of two groups. Pairs of patients that share the same household before and immediately after the first diagnosis are assigned to one group, and pairs that do not fit these criteria are assigned to the other

group. In the second method, an attempt is made to distinguish a genetic disease with a definite age association from one in which environmental factors appear to be important by comparing the age and time intervals between diagnoses of familial members. Although both methods have limitations, they can be important in studying the epidemiology of certain chronic diseases. (5 refs.)

77-1763 The Influence of Finite Observation Periods on Familial and Chronic Disease Epidemiology (Letter to Editor). (Eng.) Mantel, N. (Biostatistics Center, George Washington Univ., 7979 Old Georgetown Road, Bethesda, MD 20014) Blot, W. J. *J Natl Cancer Inst* 58(1): 10-11; 1977.

The oversimplified approach of previous authors to the use of finite observation periods in Hodgkin's disease patients, which requires both members of a familial pair to develop the disease within a restricted period of observation, is disputed. The method does not compensate for biologic, medical, or other realities. Hodgkin's disease incidence rates are influenced by age, sex, and other factors. Competing risks can interfere with the occurrence of the disease, and other considerations may limit awareness of the disease in a familial pair. The early or late occurrence of Hodgkin's disease depends on the characteristics of the family member at risk. The use of the method in situations in which the typical interval before onset of disease is short and in which no important systematic differences occur in incidence rates is not disputed. A short, typical interval would rule out rare diseases. (no refs.)

See also:

- * (Rev.): 77-1209, 77-1215, 77-1216, 77-1217, 77-1219, 77-1220, 77-1223, 77-1225, 77-1227, 77-1229, 77-1232.
- * (Chem.): 77-1290, 77-1386, 77-1391, 77-1416.
- * (Phys.): 77-1422, 77-1423, 77-1428, 77-1434, 77-1437, 77-1540.
- * (Path.): 77-1706.

MISCELLANEOUS

- 77-1764 The Analysis of Malignancy by Cell Fusion. VII. Cytogenetic Analysis of Hybrids Between Malignant and Diploid Cells and of Tumours Derived from Them.** (Eng.) Jonasson, J. (Sir William Dunn Sch. Pathology, Univ. Oxford, Oxford OX1 3RE, England) Povey, S.; Harris, H. *J Cell Sci* 24: 217-254; 1977.

A series of hybrids between malignant and diploid mouse cells and the tumors produced by these cells were subjected to cytogenetic analysis. Malignant cells were crossed with diploid fibroblasts and lymphocytes. The tumor-producing ability of the malignant cells was significantly decreased following fusion with diploid cells. With continued cultivation, the ability of the hybrid cells to generate progressive tumors returned. Studies of biparental melanoma \times diploid cell crosses showed that the elimination of chromosome 4 and the duplication of chromosome 15, from either of the parent cells, is a constant feature of these hybrids. In hybrid cells, selection pressure against chromosome 4 discriminates between the diploid and malignant homologs, suggesting that the activity of a crucial locus on this chromosome is in some way changed in both the melanoma and fibrosarcoma homologs. A discrimination between malignant and diploid homologs was not observed for any other chromosome. Elimination of both copies of chromosome 4 did not relieve the suppression of the malignant phenotype. Several hybrids from which both homologs of this chromosome had been eliminated in vitro remained unable to produce progressive tumors. The results suggest that the reappearance of malignancy requires the intervention of some additional event besides the elimination of both copies of chromosome 4. (26 refs.)

- 77-1765 The Analysis of Malignancy by Cell Fusion. VIII. Evidence for the Intervention of an Extrachromosomal Element.** (Eng.) Jonasson, J. (Sir William Dunn Sch. Pathology, Univ. Oxford, Oxford OX1 3RE, England) Harris, H. *J Cell Sci* 24: 255-263; 1977.

Several hybrids between clone PG19 mouse melanoma and diploid human fibroblasts and lymphocytes were selected for detailed study. These hybrid clones were karyotyped, and their ability to generate progressive tumors in nude mice was studied. Inoculations of 5×10^4 or 2×10^6 hybrid fibroblast cells per mouse failed to produce any tumors in nude mice. The malignancy of the mouse melanoma was suppressed by the human diploid cell, despite the fact that there is preferential elimination of human chromosomes in these hybrids. Clone 19 HAT, a subpopulation of lymphocytes in which the human x chromosome was retained by growth in HAT medium, and clone 19 6TG, in which the X chromosome was removed by growth in thioguanine, were less tumorigenic than clone PG19 itself. Clone 21, a triparental hybrid clone containing two PG19 chromosome sets and approx 12 human

chromosomes (including the X), also showed a greatly reduced incidence of tumor formation compared with clone PG19. The suppression produced by fibroblasts was more profound than that produced by lymphocytes. The tumor-producing ability of hybrids constructed from clone PG19 and irradiated diploid human fibroblasts was lower than observed with clone PG19 alone, but the tumor-forming ability of these cells was substantially higher than that seen with hybrids formed from clone PG19 and unirradiated human diploid fibroblasts. The results suggest that the suppression of malignancy involves the activity of some radiosensitive, extrachromosomal element. (19 refs.)

- 77-1766 Cell Fusion Studies with Mouse Myeloma Cells and Human Lymphoblasts or Fibroblasts (Meeting Abstract).** (Eng.) Seravalli, E. (Sloan-Kettering Inst. Cancer Res., New York, NY 10021) Charry, I.; Velivasakis, M.; Hershberg, A.; Campana, T. *Fed Proc* 36(3): 1195; 1977. (no refs.)

- 77-1767 Genetic Characterization of Methotrexate-resistant Chinese Hamster Ovary Cells.** (Eng.) Flintoff, W. F. (Dept. Bacteriology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada) Spindler, S. M.; Siminovitch, L. *In Vitro* 12(11): 749-757; 1976.

Some of the genetic properties of methotrexate-resistant (Mtx) Chinese hamster ovary cells (CHO), which had been selected and partially characterized previously, were determined. Three distinct stable phenotypes had been isolated from the Mtx-resistant CHO. Class I cells contain an apparent structural alteration in dihydrofolate reductase; Class II cells have an alteration affecting the permeability of the drug; and Class III cells, selected from Class I cells, have an increased activity of the altered enzyme. The spontaneous mutation rate to Class I resistance was approx 2×10^{-9} mutation per locus per generation. In single-step mutagenized selections, the number of resistant colonies of Classes I and II was the same. In somatic cell hybrids between Mtx-resistant and -sensitive cells, the Class I and III markers were expressed as codominant traits, and the Class II marker was expressed as a recessive characteristic. Since Classes I and III behave codominantly, it should be possible to isolate these mutants from all cell strains, including strictly diploid fibroblasts. (25 refs.)

- 77-1768 Increased Effect of a Transmissible Entity on the Control of Cancer in C₃H/St Mice.** (Eng.) Strong, L. C. (Leonell C. Strong Res. Foundation, Incor-

porated, 10457-1 Roselle St., San Diego, CA 92121) Matsunaga, H. *J Surg Oncol* 9(1): 99-103; 1977.

An evaluation was made of the growth of spontaneous tumors obtained in mice through 22 generations of lineal descent after the injection of a liver extract into a parent with a spontaneous tumor at that number of generations removed from the same descent. A total of 371 inbred C₃H/St mice bearing spontaneous tumors of mammary gland origin were used. None of the derived descendants of a mouse that had received an injection of liver extract had ever received any treatment of their mammary gland-derived tumor. The maximum effect of the transmissible entity was the complete suppression of cancer growth through, at least, the 25th period of observation. A second sudden reversal of effect on cancer growth was indicated after 15 generations of inbreeding following the appearance of the transmissible entity. The alteration changed the growth of cancer from a very low effect to a maximum effect. Without resorting to any outcross, the effects of the fate and growth of spontaneous tumors of mammary gland origin in mice can be obtained in a single lineal descent of C₃H/St inbreds. (5 refs.)

77-1769 **An Animal Model for the Growth of Human Tumor Cell Lines.** (Eng.) Oldroyd, R. I. (Univ. Oregon Health Sciences Center, Div. Urology, Portland, OR 97201) Poole, R. R.; Reed, R. R.; Lawson, R. K.; Hodges, C. V. *Invest Urol* 14(6): 434-439; 1977.

The development of an animal model that could be handled easily, without special environmental control, and that would yield good tumor growth with a variety of tumors is described. Six Lewis and Brown Norway rats were thymectomized at < 24 hr of age and inoculated ip with 0.10 ml anti-lymphocyte serum (ALS) 24 hr before day-1 sc injection of 2×10^6 heterologous human tumor cells. Three rats were given cell line T-24, a transitional cell carcinoma of the urinary bladder, and three were given line MA-160, a benign prostatic hyperplasia. ALS was also given on days 0, 1, and, hereafter, in 2- to 3-day intervals, to day 17; the dosage was increased gradually to 0.20 ml. After day 17, ALS was given twice a week at a dose of 0.25 ml. Palpable nodules were first noted on day 3; by day 10, the largest nodule measured 7 × 3 mm, with the remaining nodules averaging 4-6 mm in greatest diameter. All animals except one continued to show progressive tumor growth, and they were sacrificed at various intervals. All the sacrificed rats had metastatic disease either to the sc lymph nodes, the mesenteric lymph nodes, or the lung. The T-24 tumors grew in a distinctive pattern consistent with transitional cell bladder carcinoma, but the MA-160 tumors formed a homogeneous tumor mass. This model may be applicable to the study of a wide variety of genitourinary tumors. (13 refs.)

77-1770 **Explant Cultivation of Normal and Neoplastic Human Prostatic Gland Tissue (Meeting Ab-**

stract). (Eng.) Malinin, T. I. (Univ. Miami and VA Hosp., Miami, FL 33152) *Fed Proc* 36(3): 1066; 1977. (no refs.)

77-1771 **Tumor Production in Nude Mice by Cultured Human Tumor Cell Lines (Meeting Abstract).** (Eng.) Fogh, J. (Sloan-Kettering Inst. Cancer Res., Rye, NY 10580) Fogh, M.; Orfeo, T. *Fed Proc* 36(3): 1086; 1977. (no refs.)

77-1772 **Sarcomas Routinely Produced from Putatively Nontumorigenic Balb/3T3 and C3H/10T1/2 Cells by Subcutaneous Inoculation Attached to Plastic Platelets.** (Eng.) Boone, C. W. (Cell Biology Section, Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20014) Jacobs, J. B. *J Supramol Struct* 5(2): 131-137; 1976.

Tumor production by the Balb/3T3 and C3H/10T1/2 cell lines was studied. Tumors arose in 6/8 mice implanted with plastic platelet-attached Balb/3T3 cells within 8-12 wk and in 10/27 mice implanted with plastic platelet-attached C3H/10T1/2 cells within 14 wk. Tumors arising in (BALB/c × C57BL/6)F1 hybrids implanted with substrate-attached Balb/3T3 cells were found to be transplantable to BALB/c mice but not to C57BL/6 mice. Scanning electron microscopy of Balb/3T3 cells and the derived tumor cells on Teflon substrates revealed that the two cell types were remarkably similar in appearance, except that the tumor cells were larger and demonstrated many more microvilli that tended to concentrate over the nucleus. The tumors exhibited unique transplantation-rejection antigens that did not cross-react with each other. The cultured Balb/3T3 tumor cells demonstrated loss of both anchorage dependence and postconfluence inhibition of proliferation. It is concluded that Balb/3T3 and C3H/10T1/2 cells are preneoplastic and that they give rise to spontaneously transformed clones when implanted in vivo attached to a solid substrate. (28 refs.)

77-1773 **Local Vs Systemic Factors in Control of Tumor Inocula.** (Eng.) Karakousis, C. P. (Dept. General Surgery (UGI/B), Roswell Park Memorial Inst., Buffalo, NY) Douglass, H. O.; Paolini, N. S.; Evans, J. T.; Goldrosen, M. H. *Surg Forum* 27: 144-147; 1977.

The significance of the relationship between the "take" of a tumor inoculum and the local interaction with the host's tissue or the systemic factors generated in response to the tumor is assessed. Sarcoma T241 and B-16 melanoma cells, cultured in RPMI 1640 medium with fetal calf serum, were injected sc in an 0.1-ml volume into 6- to 8-wk-old C57BL/6J mice. Mice received a given number of cells injected into one site (X), 10 sites (total of 10X cells), or a tenfold increment of cells into the single site (10X). Animals who received tumor cells in only one site received injections of culture medium

alone into the other nine sites. Three groups (1 site: X, 10 sites: 10X, 1 site: 10X) of 10 mice each were injected in each T241 series, with X equaling 5×10^2 , 10^3 , 5×10^3 , and 10^4 cells, respectively. The right upper flank (RUF) was the single injection site. Furthermore, 10 mice with injections of 10^3 cells in the right medial thigh (RMT) were compared to 10 mice who received each two injections: 10^3 cells in the RMT and 10^4 cells into the left medial thigh (LMT) and to 10 mice with 10^3 cells in each of 10 sites. B-16 melanoma was injected as above in one series of 11 mice per group. Five animals who received 10^3 cells in the RUF were compared to five who received 10^3 cells in the RMT and five who received 10^3 cells in the RUF and 10^4 cells in the left upper flank (LUF). Within the multiply injected groups, the tumor appeared more often in the RMT than in the RUF, which appeared to be significant for both T241 and B-16. On day 30 postinoculation of T241, there were 19/40 palpable tumor nodules in RUF's of singly injected mice vs 7/37 in the multiply injected group. In the B-16 mice, palpable tumors appeared in the RUF's of 2/11 animals in both singly and multiply injected groups. The number of tumor nodules in the RMT's was 18/20 singly injected animals vs 20/20 multiply injected animals. Single injections of 10^3 B-16 in the RMT "took" better (3/5) than single injections in the RUF (0/5). In five mice injected with B-16 10^3 RUF and 10^4 LUF simultaneously, there was no tumor growth in the RUF, but 3/5 tumors became palpable in the LUF. In three groups of mice injected with 10^3 in RMT, $10^3 \times 10$, and 10^3 RMT + 10^4 LMT, 7/10 implants grew in the 10^3 group, but 6/10 RMT implants grew in the multiply injected group. There were significant differences in tumor takes at various sc sites. (no refs.)

- 77-1774 **Experimental Gastric Cancer in Rats.** (Fre.) Santini, R. (Laboratoire de Physiologie-Pharmacodynamie, INSA, 20 avenue A. Einstein, 69621 Villeurbanne, France) Dumas, J.; Penaud, J.; Thouvenot, J. *C R Soc Biol* 170(6): 1231-1235; 1976.

A group of 50 Wistar rats was used to study four techniques for implantation of Walker carcinoma 256 in the gastric antrum: (A) fixation of a 4×4 mm tumor fragment on the serosa of the antrum; (B) intraluminal injection of 1 cc of a cellular suspension (30,000-50,000 cells/ μ l) followed by clamping of the antrum; (C) intraparietal injection of 0.1 ml of the cellular suspension described in method (B) using a fine intradermal needle; and (D) injection of a suspension of cells followed by clamping of the antrum. Although the number of animals developing tumors was highest with method A, the tumor developed as an external growth on the serosa, and the animals survived < 1 wk after implantation. The best method was C, with tumors growing in 84% of injected rats and survival of 12-16 days. (5 refs.)

- 77-1775 **Survival of VX2 Carcinoma Cells In Vitro (Letter to Editor).** (Eng.) Galasko, C. S. (Orthopaedic Unit, Dept. Surgery, Royal Postgraduate Medical Sch.,

London W12 OHS, England) Haynes, D. W. *Eur J Cancer* 12(12): 1025-1026; 1976.

Several experiments were conducted to determine if the VX2 carcinoma could be maintained in vitro. Ampules of tumor cell suspensions were prepared by finely dividing a piece of tumor and filtering it through gauze. In the first experiment the ampules were placed in ice, and at intervals of 24, 48, and 72 hr the tumor suspension was injected into the thigh muscles of New Zealand white rabbits. In the second experiment ampules were frozen in liquid nitrogen. Injections were given at intervals varying from immediately after freezing to 4 wk later. In the final experiment 10% dimethyl sulfoxide (DMSO) was added to the medium, and the suspension was stored at -70°C until needed. The cells formed a fibrin clot that was implanted into the thigh muscle at intervals varying from 4 hr to 13 mo. All suspensions except those stored in liquid nitrogen produced tumors that were histologically identical to the normally passaged tumors. The results indicate that VX2 carcinoma can be stored in vitro and does not require passage from one animal to another. (4 refs.)

- 77-1776 **The Effect of Surgical Biopsy on the Cell Production Rate of a Murine Tumour.** (Eng.) Baxter-Smith, D. (Dept. Anatomy, Medical Sch., Birmingham, England) Thomas, D. B.; Riches, A. C. *Br J Surg* 63(12): 984-987; 1976.

The cell production rate of a mammary adenocarcinoma after surgical biopsy was assessed in syngeneic CBA/Birmingham mice of both sexes, 8-14 wk old. Tumor cell proliferation was monitored using vincristine sulfate (2 mg/kg ip) as a metaphase arrest agent. Groups of mice were implanted with tumor samples from seven different generations of the source tumor. The av cell proliferation rate was 24.7 metaphases/1,000 cells/hr and was independent of source generation. This rate also remained constant for different tumor volumes (24 metaphases/1,000 cells/hr). To determine the effects of biopsy, mice were implanted with tumor samples, and approximately half of the tumor mass was removed under anesthesia when the tumor reached about 18 mm in diameter (days 11-12). Untreated anesthetized controls and sham-resected anesthetized controls were included. Biopsy produced an immediate decrease in cell production to an av value of 10.3 metaphases/1,000 cells/hr, followed by a gradual recovery over 48 hr to control levels (25.3 metaphases). The rate remained at control levels up to 120 hr after biopsy. Anesthetized control and sham-resected anesthetized controls did not differ from untreated controls. Biopsy of one tumor in mice bearing bilateral sc inguinal implants reduced the preresection values of 26.4 and 26.7 metaphases for the left and right implants, respectively, to 4-yr postbiopsy (left side) levels of 11.8 and 12.1 metaphases. The cell proliferation rate was restored to control values by 48 hr postoperatively. Hematological and vascular parameters may be factors influencing cell production after surgery. (17 refs.)

7-1777 **Paradoxical Growth of Nontumorigenic Cells Within Millipore Diffusion Chambers in Mice (Meeting Abstract).** (Eng.) Reid, L. C. (Univ. California, San Diego, La Jolla, CA 92093) Stiles, C. D. *Fed Proc* 36(3): 1087; 1977. (no refs.)

7-1778 **The Kinetics of Cell Growth with a Simple Modified Algire Chamber and a Technique for Cancer Cell Subculture (Meeting Abstract).** (Eng.) Ryoo, J. (Pulmonary-Allergy Section, Medical Dept. Creighton Univ. Sch. Medicine, Omaha, NB 68131) Brody, A. W.; Chiriak, M. Z.; Moshier, S. E.; Johnson, J. R. *Fed Proc* 36(3): 1087; 1977. (no refs.)

7-1779 **Early and Late Volume Changes During Erythroid Differentiation of Cultured Friend Leukemic Cells.** (Eng.) Loritz, F. (Dept. Medical Biophysics, Univ. Toronto, Toronto, Ontario, Canada M4X 1K9) Bernstein, A.; Miller, R. G. *J Cell Physiol* 90(3): 423-437; 1977.

The kinetics of the induction of Friend erythroleukemic cells (FLC) by in vitro addition of dimethylsulfoxide (DMSO) was studied by measurement of cell volume, volume coefficient variation and cell-doubling time. Two distinct volume changes were observed. An early change, which occurred 10 days after addition of DMSO, consisted of a 10-20% decrease in volume compared to untreated cells. This decrease persisted for 2 days and was proportional to both the concentration of DMSO and the number of differentiated cells seen on day 10. This early volume shift was reduced or absent in several Friend FLC lines which induced weakly or not at all with DMSO. The exact time of the early volume change is a function of cell growth and appears to be cell-cycle related. This change in cell populations exposed to DMSO during G₂ and G₁ phase occurred after one round of mitosis and after two rounds in cells in the G₂-M phase. A later, more gradual increase in volume was observed in cultures that began to produce Hb after about five doubling times. Only a portion of the cell population became smaller in size. One of the earliest physical changes during the induction of FLC by a chemical, is the decrease in modal cell volume. (32 refs.)

7-1780 **On the Relationship Between the Activity of Acetylation, Growth of Experimental Tumors and the Efficacy of Their Suppression by Hydrazine Sulphate.** (Eng.) Dilman, V. M. (N. N. Petrov Res. Inst. Oncology, Endocrinology, 68 Leningradskaya St., Pesochny-2, Leningrad 188 646, USSR) Anisimov, V. N.; Kolosov, A. I.; Gerasimovskaya, L. N. *Oncology* 33(5/6): 219-221; 1976.

The increase in N-acetyltransferase activity was evaluated as an indispensable feature of neoplastic growth. Female rats and SHR mice were inoculated with carcinosarcoma Walker-

256, sarcoma-45, Pliss' lymphosarcoma, a fast-growing strain of thyroid tumor (rats), and solid sarcoma 180 (mice) by sc injection of 0.2 ml of tumor cell suspension in saline. The acetylation rate increased in the rats with Walker-256, sarcoma-45, and lymphosarcoma following transplantation. Malignant growth involved the activation of sulfadimidine acetylation in both rats and mice. Single doses of hydrazine sulfate (60 mg/kg body wt sc for 10 days, starting on day 3 after tumor inoculation) inhibited Walker-256 88%, Pliss' lymphosarcoma 58%, thyroid tumor 98%, and sarcoma-180 36%, but it failed to affect sarcoma-45 in rats. The treatment did not result in any increase in acetylation activity associated with tumor growth in rats with Walker's carcinosarcoma, and the acetylation rate was found to be below the original value at the end of the experiment and showed a 39.4% decrease, as compared with controls when tumor growth was inhibited by 88%. The inhibition of sarcoma-180 by 36% in mice was matched by a 29.4% decrease in the acetylation rate. There was no decrease in acetylation level when treatment failed to suppress the growth of sarcoma-45. Hence, both in rats and mice tumor growth inhibition involved a decrease in acetylation activity whereas acetylation activity did not decrease when hydrazine sulfate did not cause suppression. (20 refs.)

77-1781 **The Effect of Psychic Stress on Mice with Intraperitoneally Transplanted Ehrlich Ascitic Tumors.** (Cro.) Pajntar, M. (Institut za Histologijo in Embriologijo Medicinske Fakultete, Univerze v Ljubljani, 61105 Ljubljana, Yugoslavia) Zorc, M.; Kalisnik, M.; Vraspir-Porenta, O.; Logonder-Mlinsek, M. *Libri Oncol* 5(2): 23-29; 1976.

The effect of psychic stress, of same intensity but for different periods of time, on the growth of transplanted Ehrlich ascites tumor (EAT) in mice was studied. Also, the effect of this induced stress in the adrenal glands was evaluated. Ninety-seven adult CBA mice were inoculated ip with 10⁷ cells of EAT. The control group (A) was not exposed to stress, but the other three were: Group B, from the time of transplantation, and Groups C and D for 2 and 4 wk, respectively, before transplantation until death. The stress was induced by flashes of light followed by weak electric shocks (15-min intervals, 6 hr/day, 5 days/wk). The effect of this stress on the adrenal glands was studied over a 5- to 7.5-mo period in five female albino mice. The Group C mice lived longer than those in Group A (C:x = 16.8 days; A:x = 12.6 days; t = 2.68, P < 0.02). The survival rate was higher among the male animals in Groups B-D, which lived 4.7 days longer than Group A males. Female mice from the experimental groups lived 3.5 days longer than female controls. The adrenal glands in the animals under stress had a significantly greater density of blood vessels in general and vacuoles in the fascicular zone, and a smaller density of giant cells in the x zone. The animals under stress lost wt, which indicates a changed equilibrium between the anabolic and catabolic hormones in favor of the latter. (11 refs.)

- 77-1782 Correlation Between the Circadian Rhythms of Division and Tissue Functions in the Liver of Rats in Normal and Precancerous States.** (Eng.) Barbason, H. (Laboratoire d'Anatomie Pathologique, Université de Liege, 1, rue des Bonnes Villes, B-4000 Liege, Belgium) *Acta Histochem (JENA)* 161: 99-108; 1977.

The kinetics of the division and differentiation functions of the rat liver were compared to determine the gene regulatory mechanism of their nycthemeral activities. As a measure of these functions, the mitotic index and cholesterol-7, α hydroxylase activity were determined during regeneration in normal and partially hepatectomized (PH) rats. These parameters were also compared when PH was performed at different times. In addition, a chalone solution was injected into the rats 1 and 6 hr after PH. These rats were then treated chronically with diethylnitrosamine (DEN) in the drinking water, and the chalone and demethylase activities of the precancerous liver were tested at different stages. The results show that division and differentiation are mutually exclusive. The genes coding the enzymes of these two functions are derepressed in a complementary fashion at two different times of the nycthemeral. This cell kinetics evolution could be related to the chalone homeostatic regulatory mechanism, in which corticoids probably act as effectors. During the precancerous stage, however, the two functions are damaged and unbalanced, and their nycthemeral rhythm is lost. This is due to the loss of chalone activity. The most important transformation induced by DENA was the breakdown of the chalone homeostatic regulatory mechanism. (20 refs.)

- 77-1783 Onset of Cell Proliferation in the Shortened Gut. Rapid Hyperplasia After Jejunal Resection.** (Eng.) Obertop, H. (Surgical Services, Shriners Burn Inst., Boston, MA) Nundy, S.; Malamud, D.; Malt, R. A. *Gastroenterology* 72(2): 267-270; 1977.

The early manifestations of cell proliferation were investigated in the small and large bowel of young female Sprague-Dawley rats following resection of the proximal one-third of the small bowel. There was a pronounced increase in RNA content of the mucosal scrapings from the mid-small bowel 2 days after jejunectomy and a significant, but less marked, increment in scrapings from the ileum. In the ascending colon, although the RNA content in the mucosa from resected gut was 6% lower than that from controls, it was 21% greater than that from transected gut, an increment similar to that found in the mid-small bowel. After the second day, the mucosal RNA content was significantly increased only in the mid-small bowel. There was an increased absolute or relative DNA content in every segment of the small and large bowel, except the descending colon, on the second day after jejunectomy. After this time, significant increases in DNA were present only in the small bowel, principally the mid-small bowel. Increased amounts of DNA radioactivity after injection of H³-thymidine were observed only at 2 days after jejunectomy,

when there was an increase of 114% in the mid-small bowel from resected gut compared with transected gut, and at 5 days after jejunectomy, when the increase was 35%. The DNA specific activity was increased in comparison with specimens from transected gut only in the mid-small bowel on the second postoperative day. It was the same as that in transected gut on the 5th and 7th days, but fell 33% on the 10th postoperative day. Stimulated cell proliferation in the distal gut begins immediately after jejunectomy but the nucleic acid contents of the midgut mucosa increase within 2 days (39 refs.)

- 77-1784 Cell Movement as Related to Oncogenesis** (Eng.) Barski, G. (Laboratoire de Culture Tissus, Gustave-Roussy, F-94800 Villejuif, France) Leon, B.; Lefrançois, D.; Belehradek, J. *Blood Cells* 2(3): 453-466; 1976

Phase contrast and time-lapse microcinematography was used to illustrate the evolution of the morphology and behavior of mouse-lung cell cultures in vitro. The cultures, which at the start displayed a heterogeneous population of connective tissue cells, evolved toward a more homogeneous population (transformation). Dramatic departures occurred from the diploid karyotype. The evolution from a low cancer to a high cancer cell population (as with P4bis and P4bisT cell lines) was accompanied by morphologic and behavioral changes that were easily recognized by cinematography. The increased, sometimes explosive mobility of the cytoplasm, the cytoplasmic membranes and their processes appeared to be correlated with a changed energy balance of the cell after transformation. The changes in mobility were also correlated with the relative ease with which individual cells detached from the bulk of the tumor nodule. Certain cell structures such as heart tissue, resisted invasion longer than fibroblasts. Malignant transformation results in a cell phenotype characterized by essentially modified functions of the cell surface, the cell membrane in particular, and presumably involved modified proteins that are instrumental in these changes. (1 refs.)

- 77-1785 Rat Glioma Cells (C₆) Cultured in Serum-free Defined Medium.** (Eng.) Fan, K. (Lab. Service Veterans Admin. Hosp., Shreveport, LA 71130) Uzman, I. G. *Exp Cell Res* 106(2): 397-401; 1977.

Morphological differentiation with extended dendrite processes was observed in rat glioma C₆ cells adapted to and maintained in serum-free medium for 11 mo. The phenomenon was reversible by resupplementation of serum and was protein- or RNA-synthesis-dependent. The addition of cyclophosphamide or vinblastine sulfate to serum-free cultures caused the extensive dendrite processes to retract rapidly and completely. Dibutyryl cyclic AMP was able to stimulate the extension of cytoplasmic processes of cells cultured with serum but no further stimulation was observed in cells adapted to

serum-free medium. The serum-free adapted cells retained the ability to synthesize the acidic S-100 protein at a production rate 25% higher than the cells cultured in serum-supplemented medium. The serum-free adapted cells had a longer population doubling time but the metaphase chromosomes showed the same karyotype and modal number as that of C₃ cells continuously cultured in serum-supplemented medium. (17 refs.)

77-1786 Cell Cycle Changes in Transformed Cells Growing Under Serum-free Conditions. (Eng.) Bush, H. (Dept. Pathology, NYU Medical Centre, New York, N. Y. 10016) Shodell, M. *J Cell Physiol* 90(3): 573-583; 1977.

A study is presented of the behavior of polyoma transformed baby hamster kidney cells (PyBHK) and SV40 transformed mouse cells (SV3T3) transferred in culture using crystalline trypsin followed by neutralization with soybean trypsin inhibitor. Both cell lines proliferated freely in defined, nutritionally adequate, medium (Waymouth's) without any serum supplement and without any intervening period of adaptation. While cells continued to divide for up to 6 days, the rate of growth was slower than after addition of serum. Addition of 0.5% or 2.0% serum led to increasing rates of cell growth. Irrespective of the prevailing rates of growth, percentages of cells synthesizing DNA were the same. However, the rate at which DNA was being synthesized changed proportionately with the changes in overall growth rate. These results show that serum is not necessary for the cultivation of SV40-virus transformed 3T3 or polyoma-virus transformed BHK cells. (27 refs.)

77-1787 Differences in Membrane Structure Between Suspended and Attached Mouse Neuroblastoma Cells. (Eng.) Erkel, L. J. (Dept. Zoophysiology, Univ. Goteborg, Fack 400 33 Goteborg, Sweden) *FEBS Lett* 77(2): 187-190; 1977.

Fluorescence measurements of suspended (S) and attached (A) mouse neuroblastoma C 1300 clone 41A3 cells were made by an ordinary spectrofluorimeter. Three probes were used: (1) phenyl- α -naphthylamine (NPN), a neutral, hydrophobic probe; (2) 8-anilino-1-naphthalenesulfonic acid (ANS), an anionic probe known to bind to proteins and to membrane lipids; and (3) dansylcadaverine (DC), a probe that is believed to bind to biomembrane anionic sites. The fluorescence polarization of the penetrating probe NPN was almost the same for S and A cells, but ANS was bound more firmly to the sites of S cells than to those of A cells. The initial incorporation of both probes was largest in the S cells and reached equilibrium faster in S than in A cells. This was interpreted as being due to the more open membrane structure in S cells; ie, a conformation with easily accessible binding sites. The A cells bound a smaller proportion of ANS and greater proportion of DC than S cells. This may reflect a

more negatively charged cell surface. The results indicate that the attachment of a cell to a surface changes the properties of its membrane, although it is not possible to determine whether the observed effects reflect structural and/or electrical alterations. (7 refs.)

77-1788 Sezary-like Cells from Supernatant of Burkitt Lymphocyte Cell Culture (Letter to Editor). (Eng.) Noguchi, S. (Cleveland, OH) *Arch Dermatol* 112(11): 1612-1613; 1976.

The Sezarylike cells found in a supernatant of Burkitt's lymphocyte cell cultures are described. To 1 million lymphocytes (obtained from healthy laboratory personnel) in 1 ml of medium was added 1 ml of a cell-free supernatant of the HR-1-K line of Burkitt's lymphoma. For one control, 2 ml of fresh medium were added to the lymphocytes. A second control was identical to the first, except that the medium contained 20 μ l of phytohemagglutinin (PHA) throughout the experiment. During the second week of incubation, the cells with the HR-1-K supernatant had transformed and were actively proliferating. In the controls, the number of cells decreased to 10% of the starting number. On day 14, the transformed cells were studied for morphological characteristics and surface markers. Most had a highly convoluted nucleus, a high nucleocytoplasmic ratio, one or two nucleoli, and a homogeneous cytoplasm filled with ribosomes. Scattered mitochondria and cytoplasmic projections were noted. A total of 32% of the transformed lymphocytes formed E rosettes, 13% formed EAC rosettes, and 55% formed neither. Only the E rosettes were studied under the electron microscope. No clear morphological differences were noticed between rosetting and nonrosetting cells. No response of the transformed lymphocytes to PHA and pokeweed mitogen was observed when they were studied on the 18th day. After 6 wk, cells were still proliferating vigorously, but no surface markers were detectable. An immunofluorescence study for Epstein-Barr virus antigen on E-rosetting cells was equivocal. It is unlikely that the Sezarylike cells produced by the HR-1-K supernatant are responding cells to virus antigen. (8 refs.)

77-1789 Role of Tumor Angiogenesis Factor in Maintenance of Tumor-Induced Vessels. (Eng.) Faltermann, K. W. (Dept. Surgery, Children's Hosp. Medical Center, Boston, MA) Ausprunk, D. H.; Klein, M. D. *Surg Forum* 27: 157-159; 1976.

The fate of tumor angiogenesis factor (TAF)-induced vessels in the cornea following the removal of a vasoproliferative stimulus was assessed. Slow-release polymer pellets were prepared that contained 300 μ g of a TAF isolate obtained from Walker carcinosarcoma 256 grown in tissue culture. These pellets were implanted into the corneas of 25 New Zealand white male rabbits 1.5 mm from the corneal limbus. Eyes were examined every other day with a slit-lamp stereomicro-

scope. Blood flow in corneal vessels was evaluated after iv administration of 5% sodium fluorescein (0.5 ml/kg). When proliferating blood vessels reached max length, the TAF polymer implants were removed through a small corneal incision. Observations were made for 10 wk while animals were being killed serially. Thick Epon sections of corneas were examined with light microscopy. TAF-induced blood vessels grew from the vascular plexus at the corneal limbus toward the polymer implant at a rate of 0.21 mm/day until they surrounded the implant and their linear growth ceased. When implants remained in the cornea, these vessels could be maintained for as long as 60 days. When the implants were removed, the vessels began to regress. In the first week after implant removal, a dense plexus averaging 20 vessels with rapid blood flow decreased to six thinner vessels without a change in overall length. Many smaller secondary and tertiary vessel branches disappeared. After 3 wk, an av of five vessels remained, and these were thinner and paler than they were the previous week. Two to three vessels persisted until the ninth and tenth weeks while thinning to white threadlike structures barely visible with the slit-lamp. Vessels lacked flow beyond the third week. Histologically, regressing vessels first became plugged with RBC. The surrounding endothelial cells underwent vacuolation and cytolysis. During vessel degeneration, extravasated RBC were often seen. With the onset of endothelial degeneration, macrophages appeared in the perivascular connective tissue and removed the vascular cell debris. The findings support the hypothesis that tumor-induced vessels have a short half-life and require continuous stimulation by TAF. (3 refs.)

- 77-1790 **The Role of Microvilli in the Agglutination of Cells by Concanavalin A.** (Eng.) Ukena, T. E. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115) Karnovsky, M. J. *Exp Cell Res* 106(2): 309-325; 1977.

To clarify the relationship between surface morphology and agglutinability (agg), scanning electron microscopy (SEM) was used to observe the surfaces of cells growing in monolayers, detached from the substratum by EDTA, and after agglutination by concanavalin A (Con A: 100 or 500 μ g/ml). Eight cell lines of variable agg by Con A were used: 3T3-Cl-1 and -2, 3T3-Py-6-R1, mouse embryo primary cells (BALB and Swiss), SVT2, Nil-1C1, IC-21, and L929. The number of microvilli on cells growing in monolayers was correlated positively with agg. When cells were brought into suspension, however, they all developed numerous microvilli that persisted when the cells were treated with Con A, regardless of their agg. Treatment of cells with dibutyryl cyclic AMP and theophylline caused a parallel decrease in agg and the number of microvilli in monolayer cultures, but suspended cells uniformly had many microvilli, regardless of whether or not they were agglutinable. Cells that agglutinated, spontaneously, in the absence of Con A, were indistinguishable from cells agglutinated by Con A, showing a tangle of interdigitated microvilli at the points of adhesion. Surface-bound Con A was quickly withdrawn from the microvilli on all cell types. Nei-

ther the distribution of surface-bound Con A nor the morphological appearance of the cells was correlated with their agg by Con A. (38 refs.)

- 77-1791 **Biochemical and Immunological Analysis of Normal and Leukemic Lymphocyte Surface** (Meeting Abstract). (Eng.) Hilliard, J. (Baylor Coll. Medicine, Houston, TX 77030) Dreesman, G. R. *Fed Proc* 36(3): 1185; 1977. (no refs.)

- 77-1792 **Selective Labeling of Normal and Transformed Cell Surface by Trinitrobenzene Sulfonate** (Eng.) Comoglio, P. M.; Tarone, G.; Bertini, M. In: *Membranes and Disease*. Bolis, L.; Hoffman, J. F.; Leaf, A., eds (New York: Raven Press): pp. 155-162; 1976.

Cell-surface changes in baby hamster kidney (BHK) fibroblasts transformed by the B4 strain of Rous sarcoma virus were analyzed by a technique based on labeling with trinitrobenzene sulfonate (TNBS). TNBS selectively labeled the amino groups of proteins and lipids exposed on the outer surface of the plasma membrane. Neoplastic transformation was accompanied by a fivefold increase in TNBS binding groups exposed on the outer cell surface. The electrophoretic pattern for the surface proteins from normal BHK cells and B4-transformed cells was almost identical, indicating that the transformation of BHK fibroblasts is not accompanied by the appearance of one or more new proteins particularly rich in amino groups. Transformation is more likely followed by a general rearrangement of the outer surface of the membrane leading to the exposure of amino groups that are sterically inaccessible or nonreacting in the same proteins exposed on the surface of normal cells. (26 refs.)

- 77-1793 **Comparison of Hematology and Clinical Chemistry Parameters in Tumor-Bearing and Tumor-Free Mice** (Meeting Abstract). (Eng.) Denine, E. P. (Southern Res. Inst., Birmingham, AL 35205) Harrison, S. D. *Pharmacologist* 18(2): 182; 1976. (no refs.)

- 77-1794 **Characteristics of Resistance and Cross Resistance in Vivo of a Subline of P388 Leukemia Resistant to Adriamycin** (Meeting Abstract). (Eng.) Johnson, R. K. (NCI, NIH, Bethesda, MD 20014) Chitnis, M. P.; Goldin, A. *Pharmacologist* 18(2): 173; 1976. (no refs.)

- 77-1795 **Uptake and Retention of 3 H-Daunorubicin in Sublines of P388 Leukemia Resistant to Adriamycin or Daunorubicin** (Meeting Abstract). (Eng.) Inaba, M.

(NIH, Bethesda, MD 20014) Johnson, R. K.; Goldin, A. *Pharmacologist* 18(2): 173; 1976. (no refs.)

77-1796 Anticoagulant Inhibition of Tumor Cell Implantation (Meeting Abstract). (Eng.) Lione, A. P. (Dept. Pharmacology and Toxicology, Univ. Rochester Cancer Center, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY) Bosmann, H. B. *Pharmacologist* 18(2): 173; 1976. (no refs.)

77-1797 Cancer Procoagulant A (CPA) Activity in Cultured Normal and Transformed Fibroblasts (Meeting Abstract). (Eng.) Lewis, B. J. (Univ. Colorado Medical Center, Denver, CO 80262) Gordon, S. G. *Fed Proc* 36(3): 1082; 1977. (no refs.)

77-1798 Colony-Stimulating Activity in Cultures of Granulocytosis-Inducing Tumor. (Eng.) Burlington, H. (Medical Res. Center, Brookhaven Natl. Lab., Upton, Long Island, NY 11973) Cronkite, E. P.; Laissue, J. A.; Reincke, U.; Shaddock, R. K. *Proc Soc Exp Biol Med* 154(1): 86-92; 1977.

The colony-stimulating activity (CSA) of a granulocytosis-inducing tumor was studied in a Swiss albino mouse of the in the euthyroid subjects. After hypertonic saline infusion, the serum (Hale/Stoner) strain. The tumor was a mammary carcinoma that remained unchanged in morphology throughout 41 passages. Granulocytosis developed progressively with the tumor, reaching counts $> 100,000/\text{mm}^3$ in some mice. Differential WBC counts showed that granulocytes constituted 70%-80% of the total, with lymphocytes making up most of the remainder. Banded granulocytes were also increased, and no cells less mature than band forms appeared in the peripheral blood. Extirpation of 80% or more of tumor resulted in a return of WBC number toward normal, but regrowth provoked the return of leukocytosis. Monolayers originating from either a tumor mince or trypsinized suspensions consisted of mixed epitheliallike and fibroblastic cells. The cells displayed a lack of contact inhibition, a high rate of glycolytic and protein synthetic activity, and a capacity for continued propagation when passaged repeatedly. Both monolayer and suspension cultures consistently yielded CSA to the culture medium. Activity was present in successive media collections made at 3- to 8-day intervals over periods extending to 75 days. Heat (90 C, 15 min), in addition to abolishing CSA, appeared to unmask or generate inhibitor activity. The CSA associated with tumor culture was nondialyzable and, from results of studies utilizing ultrafiltration membranes, the activity was associated with a fraction having molecular wt $> 30,000$. Antibody to L cell colony-stimulating factor (CSF) completely neutralized the activity of tumor-conditioned medium at dilutions up to 1:64. Anti-

body dilution (1:128), which neutralized only 20% of the CSF of L cell-conditioned medium, still abolished 88% and 72% of the activity in tumor culture-conditioned medium. CSA was neutralized by antibody to CSF, which suggests that the material produced in tumor cell cultures is CSF. (12 refs.)

77-1799 Cancer-Induced Cytolysis of Normal Bone Marrow Cells. (Eng.) Zucker, S. (Veterans Admin. Hosp., Northport, NY 11768) *Nature* 265(5596): 736-737; 1977.

The tumor-mediated cytolysis of normal rat marrow cells was studied. Interactions between cancer cells and normal cells were evaluated by a modified cytotoxicity assay. Walker-256 carcinosarcoma cells were isolated from the ascites tumor that accumulated 7 days after ip transplantation of 1×10^6 Walker-256 cells to adult Wistar rats. Bone marrow cells ($1 \times 10^7/\text{ml}$) were labeled with $2 \mu\text{Ci } ^{59}\text{Fe}/\text{ml}$. Cytotoxicity was expressed as a function of the release index (RI). The spontaneous RI for marrow erythroblasts cultured alone was 18.5%. The increasing cytolysis of marrow cells cultured with Walker-256 cells was proportional to the tumor: marrow cell ratio. In cultures containing equal numbers (1×10^7 cells) of Walker-256 and marrow cells, the RI was 49.3%. Marrow cell viability, as determined by Trypan blue exclusion, was inversely proportional to the number of tumor cells in culture. The tumor-mediated cytotoxicity of erythroblasts required intact tumor cells. No cytolysis was noted with alcohol-treated Walker-256 cells or the supernatant from the tumor ascitic fluid. The cell sap of sonicated Walker-256 cells also had no effect on erythroblast cytolysis. When the effect of temperature on marrow RI was evaluated, no tumor-induced marrow cytolysis was observed in 24-hr cell cultures maintained at 4 C, and this activity was minimal at 25 C. Max marrow cytolysis was noted at 37 C. The progression of tumor-induced marrow cytolysis was assessed by incubating tumor and marrow cells together and measuring the RI. No significant increase in the release of ^{59}Fe from marrow cells was evident before 4 hr, but marrow cytolysis increased during the next 12 hr. A Walker-256 cancer-mediated cytolysis of ^{59}Fe -labeled rat RBC (labeled in vivo by iv injection of ^{59}Fe into rats 3 days before use of RBC) was shown. The spontaneous release (RI) of ^{59}Fe from rat RBC cultured alone was 1.5% in 20 hr. The RI of rat RBC cultured with Walker-256 cells (1:1 ratio) was 37.7%. Walker-256 carcinoma cells mediate the cytolysis of rat erythroblasts and RBC in suspension cultures by a cell-cell interaction that is temperature-dependent and independent of phagocytosis. (16 refs.)

77-1800 Functional Pathways of Pyridine Nucleotide Biosynthesis in Normal and Transformed 3T3 Cells (Meeting Abstract). (Eng.) Jacobson, E. L. (North Texas State Univ., Denton, TX 76203) Jacobson, M. K. *Fed Proc* 36(3): 713; 1977. (no refs.)

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